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# REDUCTION OF THE ALKALI METAL NORMAL SULFATES BY HYDROGEN AND AMMONIA

Viktor I. Spitsyn and M. A. Meerov

The literature data concerning the behavior of alkali metal sulfates, upon calcination in a current of hydrogen, do not appear to be completely exhaustive, and in certain cases contradict themselves.

Cobb [1] demonstrated that dry hydrogen begins to react with sodium sulfate at 530-540°, with the evolution of hydrogen sulfide. The reduction proceeds more rapidly at 900°. Tiede and Reinicke [2] determined a temperature of 700-750° for this reaction, and they noticed that inaddition to sulfide, a quantity of polysulfide was also formed; Lewis, Randall and Bychowsky [3] observed the formation of noticeable quantities of hydrogen sulfide and the sublimation of free sulfur when hydrogen was reacted with sodium sulfate in the temperature range of 220-250°. The residue gave an alkaline reaction and did not contain sulfide as a constituent. According to the data of Berzelius [4] and Regnault [5], potassium sulfate is reduced to the sulfide by hydrogen at red heat. Berthelot [6] records secondary reactions: due to interaction of the formed water, caustic alkali is formed; moreover, the residue contains potassium polysulfide as a constituent. In the escaping gaseous products are present hydrogen sulfide, water and free sulfur vapors.

Tiede and Reinicke [2], in a work devoted to the derivation and properties of the phosphorescent sodium and rubidium sulfides, studied the conditions for conversion of rubidium sulfate into sulfide by a current of hydrogen. The authors indicated that $Rb_2SO_4$ is partially reduced by hydrogen at a temperature of 500°. At the same time noticeable hydrogen sulfide evolution was observed. At 700°, the resulting sulfide vaporized rapidly. In order not to lose large quantities of the sulfide because of its volatility, Tiede and Reinicke heated rubidium sulfate in the hydrogen current for only a short time (about 5 minutes), at a temperature of 650°.

The authors (present article) did not find literature data on the behavior of the normal sulfates of the alkaline elements when calcined in a current of ammonia.

In the present work the behavior of the normal alkali metal sulfates upon heating with hydrogen and with ammonia currents was studied, and their temperature condition for reduction, was determined.

Earlier, one of us [7] described the preparation of the necessary alkali metal sulfate samples. Analysis for $SO_3$ content of the samples used was conducted by the usual method. Results are quoted in Table 1.

TABLE 1
Analysis of the Alkali Metal Sulfates

| Compound | Content $SO_3$ (%) | |
|---|---|---|
| | Found | Calculated |
| $Li_2SO_4$ | 72.81 | 72.77 |
| $Na_2SO_4$ | 56.31 | 56.34 |
| $K_2SO_4$ | 45.89 | 45.95 |
| $Rb_2SO_4$ | 31.04 | 29.98 |
| $Cs_2SO_4$ | 22.22 | 22.14 |

A weighed portion of the sample, in a porcelain boat, was placed into a second protective boat and was introduced, at room temperature, into the working tube of an electric oven. The air was then removed from the apparatus by a current of the gas in question. The oven temperature was gradually raised, and the rate at which the gas passed through was determined to be approximately equal to 6 liters per hour. After termination of the experiment, the product was also cooled in a current of the same gas applied.

The hydrogen required for the experiments was obtained by the usual procedure from a Kipp apparatus, and was dried, before entering into the working tube of the oven, by passing through Tishchenko flasks containing concentrated sulfuric acid. Gaseous ammonia was produced by heating commercial aqueous solution, and was passed through drying columns containing lumps of sodium hydroxide and calcium oxide.

Calcination of the normal sulfates of the alkali metals in a current of hydrogen has shown that all of them, including lithium and cesium sulfates, can be transformed into the sulfides at the appropriate temperatures, concerning which reduction there are no data in the literature. Thus, for example, a weighed portion of

cesium sulfate was heated in a stream of hydrogen for 1 hour at 600-620°. The product was obtained as a slightly-caked mass, with faint hydrogen sulfide odor. After removal from the tube, the sample had a yellowish color, changing rapidly in the dessicator to a greenish color, with a narrow black border around the edges of the boat. The product was analyzed. On one weighed portion, sulfate-sulfur was determined, on the second, total sulfur, according to Tredvel [8]. The sulfide-sulfur content was calculated by difference. Analysis showed that the product contained 99.15% $Cs_2S$ and 0.85% $Cs_2SO_4$. The reduction process evidently took place according to the following equation: $Cs_2SO_4 + 4H_2 = Cs_2S + 4H_2O$. Calcination of the other normal sulfates of the alkali metals in a current of hydrogen yielded analogous results. The product remaining in the boat after calcination of lithium sulfate was light-yellow in color, of the sodium sulfate — yellow-pink, and of the potassium and rubidium — brick-red, the cesium sulfate, as indicated above, — yellow-green.

Judging from the color of the described products, the reduction process for the alkali metal sulfates, using hydrogen, is actually quite complicated. Thus, in the case of the potassium and rubidium sulfates, and partially with sodium, there are undoubtedly formed the polysulfides which are red in color. The mechanism of reaction was investigated further. For the present work it was of interest only to determine reaction temperatures for the sulfates with hydrogen, in order to compare their stability under other conditions.

TABLE 2

Calcination of the Normal Sulfates of the Alkali Metals in the Hydrogen Current. Duration of each experiment 1 hour

| Temperature (° C) | Weighed portion of sample | | | | |
|---|---|---|---|---|---|
| | $Li_2SO_4$ 0.0784 g | $Na_2SO_4$ 0.2025 g | $K_2SO_4$ 0.2069 g | $Rb_2SO_4$ | $Cs_2SO_4$ 0.0396 g |
| 570 | — | — | — | — | 0.0396 |
| 600 | — | — | — | — | 0.0396 |
| 620 | 0.0784 | — | 0.2069 | 0.1386 | 0.0260 |
| 650 | 0.0784 | — | 0.2069 | 0.1386 | — |
| 670 | 0.0456 | 0.2025 | 0.1565 | 0.1218 | — |
| 700 | — | 0.2025 | — | — | — |
| 720 | — | 0.0978 | — | — | — |

The experimental results for the control series of experiments are quoted in table 2.

The calcination of the alkali-metal normal sulfates in a current of ammonia has indicated that here, too, the conversion into sulfides occurs at defined temperatures. Thus, as an illustration, the normal sulfate of cesium reduces to sulfide in the temperature range 740-770°. The rate of reaction increases sharply with increase in temperature. After calcination for 1 hour at 820°, the reduction product possessed a strong hydrogen sulfide odor and changed color rapidly in the air and in a dessicator. Upon withdrawal from the oven as brick-red, it changed in color to rose-yellow, yellow-gray, and finally into yellow-green with a black rim around the edges of the boat. Analysis showed that the final product contained 61.35% of the sulfide. The reduction of sulfates to sulfides by gaseous ammonia occurs at the expense of the hydrogen which results when the ammonia breaks down under the conditions of high temperature applied.

The calcination experimental results for the normal alkali metal sulfates are quoted in Table 3.

All products remaining in the boats, after the indicated experiments, gave off a hydrogen sulfide odor in the air. Their coloration was analogous to that of the products derived from calcination in a hydrogen current. In the case of cesium sulfate, only, the reduction product, as has already been indicated, was not a light yellow-green, but brick-red color, at the expense of the polysulfide present in considerable amount. Evidently this was related to the higher temperature for the reduction period of cesium sulfate in ammonia current, as compared with the hydrogen action.

TABLE 3

Calcination of the Alkali Metal Normal Sulfates in a Current of Ammonia. Duration of each experiment 1 hour.

| Temperature (° C) | Weighed portion of samples | | | | |
|---|---|---|---|---|---|
| | $Li_2SO_4$ 0.1346 g | $Na_2SO_4$ 0.1548 g | $K_2SO_4$ 0.1990 g | $Rb_2SO_4$ 0.1822 g | $Cs_2SO_4$ 0.0302 g |
| 670 | 0.1346 | — | — | — | — |
| 700 | 0.1346 | — | — | — | — |
| 720 | 0.1205 | 0.1548 | 0.1990 | 0.1822 | 0.0302 |
| 740 | — | — | — | — | 0.0302 |
| 750 | — | 0.1548 | 0.1990 | 0.1822 | — |
| 770 | — | 0.1214 | 0.1990 | 0.1822 | 0.0108 |
| 790 | — | — | — | 0.0758 | — |
| 800 | — | — | 0.1778 | — | — |

The abrupt temperature point at which reaction of the alkali sulfate with hydrogen beings should be noted. For example, a one-hour calcination of sodium sulfate in a hydrogen current, at a temperature of 700°, did not show any change in the weighed portion, whereas, a temperature increase to 720° led to a weight loss of more than 50% (Table 2). A weighed portion of cesium sulfate (of the 0.1 g series) showed a

weight loss of 4.8% after 1 hour calcination in a current of ammonia at 770° and at 820° – 17.2%. A comparison is given in Table 4 for the temperatures at which reaction starts between the alkali metal normal sulfates and hydrogen and ammonia.

The sulfates investigated generally reduce within closely-defined temperature conditions: 620-720° with hydrogen action, 720-800° – in the case of ammonia use. The higher temperature required for reduction by ammonia (more accurately by its decomposition products) evidently is due to the smaller concentration of hydrogen in this case.

The reduction period temperature of the alkali sulfates by hydrogen is approximately 300° lower than the temperature for noticeable thermal dissociation of the lithium and sodium sulfates, and the volatilization of the potassium, rubidium, and cesium sulfates in the air, as determined by Spitsin and Shostak [7]. In the case of ammonia, this difference is 200-230°.

Relatively speaking, sodium sulfate seems to be the most stable in the hydrogen current (beginning reaction period temperature 720°). The highest reduction temperature period for ammonia action corresponds to potassium sulfate (800°), although in this sense sodium and rubidium sulfates approach the former (Table 4).

TABLE 4
Temperature Comparison for the Reduction Periods of the Normal Alkali Metal Sulfates by Hydrogen and Ammonia

| Compound | Temperature for the Transition Period into Sulfide (° C) | |
|---|---|---|
| | In the hydrogen current | In the ammonia current |
| $Li_2SO_4$ | 670 | 720 |
| $Na_2SO_4$ | 720 | 770 |
| $K_2SO_4$ | 670 | 800 |
| $Rb_2SO_4$ | 670 | 790 |
| $Cs_2SO_4$ | 620 | 770 |

Thus, the least active, with regard to reducing agent action, appears to be the sulfate of that alkali element which stands close to the center of the group in the periodic system.

Fialkov and Shargorodsky [9] have also observed a similar change in chemical activity upon calcination of alkali sulfate mixtures with silica: potassium sulfate proved to be the most stable compound. As Spitsin and Shostak have demonstrated [7], the thermal instability is manifested only by lithium and (to a lesser extent) by sodium, at 1200°. Apparently the effect of chemical reagents (hydrogen, ammonia, silica) proves to be a more discriminating medium for experimental determination of differences in stability of the alkali metal sulfates than simple calcination.

The increase in stability of the normal sulfates upon passing from lithium to sodium or to potassium, is evidently connected with the weakening of "counterpolarization" in the compounds, due to an increase in the ionic radius of the cation. The subsequent decrease in stability, on passing to the sulfates of rubidium and cesium, may be explained by the increase in self-polarization of the ions of the alkali elements as the result of a considerable increase in their radii.

## SUMMARY

1. The reduction period temperatures of the normal alkali metal sulfates, for conversion to the sulfides, by the action of hydrogen and of ammonia, were studied.

2. It was determined that lithium, sodium, potassium, rubidium and cesium sulfates enter into the indicated reactions at close temperature conditions: 620-720° in the case of hydrogen, and 720-800° in the case of ammonia (with the respective products of decomposition).

3. As regards hydrogen, the most stable proves to be sodium sulfate, and as regards ammonia – potassium sulfate.

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* See Consultants Bureau English Translation, p. a-251.

# THE EXTRACTION OF PENTAVALENT VANADIUM FROM HYDROCHLORIDE SOLUTIONS USING ORGANIC SOLVENTS

V. I. Kuznetsov

Extraction methods for the recovery and separation of elements are, without doubt, of analytical interest, due to the rapidity and convenience of execution.

The earlier discussed [4] example of trivalent iron, where the relation between the extracting power and the structure of organic solvents was shown, indicates that there are still many uninvestigated and unutilized possibilities in this field.

In the present article, the extraction of pentavalent vanadium from hydrochloride solutions is considered, the presence of which causes complications in many analytical investigations; for this reason, the removal of vanadium from solution, or even the major portion of it, is frequently quite desirable.

Extraction recoveries of various vanadium compounds, used chiefly for qualitative reactions, are described in the literature. The compound formed from vanadium plus 8-hydroxyquinoline is extracted with chloroform [11, 13, 14], or by isoamyl alcohol. In the presence of rhodanides, vanadium is extracted by ethyl acetate [9]. The same solvent extracts vanadium diethyldithiocarbamate very fully [7].

Pentavalent vanadium is slightly extracted by diethyl ether [1] from hydrochloric acid solution, considerably extracted by amyl acetate [15], and by diisopropyl ether, with a distribution coefficient of about 0.3 [10]. The recoverability of pentavalent vanadium from hydrochloride solutions, when using diisopropyl ether, interferes with the separation of iron from vanadium, when the latter solvent is used to extract iron. Lingane and Meites [12], in this connection, have studied in detail the extraction of vanadium by diisopropyl ether, for the express purpose of determining the conditions under which vanadium does not extract. According to their data, conversion of vanadium to the tetravalent state is essential.

We considered it possible to regard the process of extraction of elements by oxygen-containing organic solvents from acid solutions as being due to oxonium-compound formation. From such a viewpoint, the varied behavior of the different classes of oxygen-containing organic compounds was to be expected.

V. V. Chelintsev [6], who studied the interaction of oxygen-containing organic subtances with $C_2H_5OMgI$, also considered this interaction to be due to the formation of oxonium compounds, and upon the heat of reaction effect, arranged the oxygen-containing organic compounds in the following order, according to their tendency to form oxonium compounds:

| $R \cdot O \cdot R <$ | $R \cdot OH <$ | $R \cdot CO \cdot OH <$ | $R \cdot CO \cdot OR <$ | $R \cdot CO \cdot R <$ | $R \cdot CO \cdot H$ |
|---|---|---|---|---|---|
| Ethers | Alcohols | Acids | Esters | Ketones | Aldehydes |

In consequence, according to V. V. Chelintsev, ethers are least inclined to form oxonium compounds, while aldehydes are the most prone.

Beside the tendency of oxygen to complex formation, the ease of oxonium compound formation undoubtedly depends also upon the individual characteristics of the organic compound, upon the nature of the acid radical, and upon many other factors. However, in the case of iron extraction from hydrochloride solution, the V.V. Chelintsev order is approximately maintained, as was earlier indicated [4], although V. V. Chelintsev determined this order from the investigation of oxonium complexes of an entirely different nature. Ethers extract iron to a lesser degree than do aldehydes or ketones.

With pentavalent vanadium, conformities to established rule proved to be more complex, but in such case the combinations with carbonyl oxygen no doubt extract vanadium more completely than do the ethers.

We have determined the distribution of vanadium between hydrochloric acid and organic solvents, in order to evaluate the ability of solvents to extract pentavalent vanadium from hydrochloric acid solutions.

3.00 ml of pentavalent vanadium solution in hydrochloric acid ($NaVO_3$ + HCl), with a content of 3.00

Table 2 and Fig. 1 will give some idea of the practical reduction rate of $V^V$ under the influence of amyl acetate, for given extraction conditions.

TABLE 2

Rate of Reduction of $V^V$ to $V^{IV}$ in Stirred Mixtures: $V^V$ (3 mg/ml), 8N HCl + amyl acetate; t = 20°.

| Time from start of test | $V^{IV}$ formed (in mg/ml) | $V^{IV}$ formed (in % of initial) |
|---|---|---|
| 0 hours | – | 0.0 |
| 0 hours 30 min | 0.06 | 2.0 |
| 1 hour | 0.075 | 2.5 |
| 2 hours | 0.15 | 5 |
| 4 hours | 0.22 | 7.3 |
| 6 hours | 0.36 | 12 |

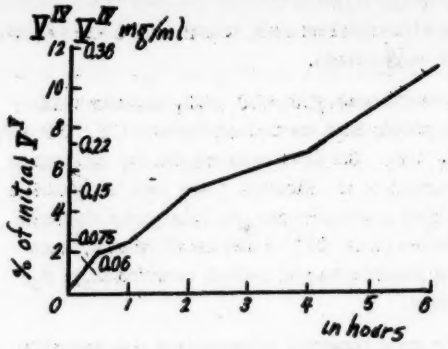


Fig. 2. Concentration increase of $V^{IV}$ in the system: 3 volumes of 8N HCl with 3 mg/ml of $V^V$ + 1 volume of amylacetate (with stirring); t = 20°.

In these, the rate of concentration increase of $V^{IV}$ is represented for a vigorously-stirred mixture of pentavalent vanadium solution, at a concentration of 3.0 mg/ml of $V^V$ in 8N HCl (3 volumes) with amylacetate (1 volume at 20°).

Since the distribution equilibrium of $V^V$ between the acid layer and the solvent layer is reached rapidly, it is desirable to carry out the extraction quickly. For example, upon recovery of $V^V$ from its solution in 8N–HCl, using amylformate, the partition coefficient was found to be equal to 9.3 with 100 shakings, and equal to 7.5 with only 5 shakings.

As can be seen, the reduction rate of $V^V$ is usually not so great. This situation permits consideration of recovery, from hydrochloric acid solutions, of pentavalent vanadium by the extraction method, to be a real possibility.

The completeness of $V^V$ recovery should not give cause for reservation, since the recovery coefficient of $V^V$ from 9N–HCl, using amylacetate, is close to the recovery coefficient of iron, using diethyl ether.

The latter method is considered to be acceptable in analysis, and so, from the viewpoint of incomplete iron extraction, there are no particular grievances to present.*

## Analytical Potentialities

The optimum conditions for possibly more complete extraction of vanadium can be formulated in the following manner. The vanadium should be in the pentavalent state. It is essential to extract from hydrochloric acid which is not less than 8N. In order not to lower the hydrochloric acid concentration, particularly during the course of multiple extractions, it is useful to saturate the solvent beforehand with hydrogen chloride, by stirring with fuming hydrochloric acid.

Amylacetate, amylformate, or their mixture with acetophenone, can be used for drastic recovery of pentavalent vanadium. The work should be carried out as rapidly and at as low temperature as is possible, carrying out repeated extractions if necessary.

For recovery of vanadium from small volumes, the work can be done in an ordinary test tube, using a capillary with a rubber (pear-shaped) syringe for removal of the organic solvent layer. Complete extraction can be carried out within a few minutes.

If recovery is carried out with small portions of solvent, then practically complete vanadium recovery can be attained with a loss of about one and one-half times the volume of solvent per volume of solution extracted (Table 3).

For evaluation of the potentialities for application of the described extraction methods for the separation of elements, there should be taken into account the general rule of element extraction by oxygen-containing

* It should be noted that in the case of iron, the incompleteness of iron recovery is also conditioned by the reduction of extractable $Fe^{III}$ to non-extractable $Fe^{II}$. In this connection, a search was carried out for a solvent more resistant to oxidation than ordinary diethyl ether, and as a result, substitution of the less easily oxidized diisopropyl ether for diethyl ether has been recommended [8, 10].

organic solvents.

If it is considered that transferral of elements from the hydrochloric acid layer to the organic solvent layer is related to the formation of compounds of the oxonium salt type, it is reasonable to assume that only anions, and not cations, can be extracted.

But apparently among anions, too, all are not extracted to the same degree. Metal complex ions, of the type $MeHal_n^{m-}$, containing halogens, and their analog rhodanide extract well. The rhodanide metal complex anions extract particularly well.

TABLE 3

The comparative extraction of pentavalent vanadium from pure solutions of $NaVO_3$ + HCl; t = 20°.

The original solution contained 18 mg of $V^V$ in 6 ml of 8 N HCl. Seven consecutive extractions, 1.5 ml of solvent for each were carried out. The solvent was removed with a capillary

| Recovery results | Solvent | |
|---|---|---|
| | amylacetate | amylformate |
| Vanadium ($V^V$) remaining in total volume | 0.02 mg | Not found (i.e. $<$ 0.003 mg) |
| $V^{IV}$ remaining in total volume | 0.09 mg | 0.06 mg |
| Percentage vanadium recovery with regard to initial quantity | 0.45% | 0.3% |
| Percentage vanadium recovery | 99.45% | 99.7% |

The extractability of one or another element is determined mainly by its ability to form only slightly dissociated complex anions, under the conditions of extraction. Because the iodides, or rhodanides, have greater capacity for complex anion formation than do chlorides, a greater number of elements are extracted in the presence of iodides or rhodanides than in the presence of chlorides alone.

It can be assumed that the very fact that an element can be recovered from hydrochloric acid solution which does not contain other reagents is an indication that the element may exist in the form of a complex anion, under the conditions of extraction. Thus the ability of elements to be extracted is characteristic for the elements which give the reactions, and requires the presence of the elements in anionic form. For example, as studied elsewhere [2], the ability of a series of elements to give color reactions with colored organic cations is based upon the formation of complex ions by the elements. Color reactions of this type also give a greater amount of elements in the presence of iodides or rhodanides, than in the presence of chlorides alone.

The ability of some elements to precipitate in the form of complex anions by the action of organic bases, of which these color reactions are found to be particular cases, is directly related to the degree of extractability of the elements by oxygen-containing organic solvents. For example, the readily-precipitating anions of $BiI_4^-$, $CdI_4^=$ have the capacity for being extracted.

This relation is favorable in practice, since the presence of reactions of one kind permits the assumption of the possibility for the existence of a reaction of another type, also. From the ability to precipitate and to give color reactions with colored organic cations the extractability tendency can be judged, and vice versa. The only prerequisite is the consideration of different conditions for completion of reaction; the color reaction, and precipitation, are usually completed at relatively low acidity, and during extraction the acidity is very high. Under such differing conditions, one and the same element may form ions of different composition and character.

## SUMMARY

1. It is possible to effect practically complete recovery of pentavalent vanadium from hydrochloric acid solutions by extracting vigorously with oxygen-containing organic solvents, for example the esters (amylacetate, amylformate), or acetophenone.

2. Aliphatic ketones extract $V^V$ better, but reduce $V^V$ to $V^{IV}$ too rapidly. The completeness of extraction is limited by the partial reduction of pentavalent vanadium into the non-extractable tetravalent state.

3. The extraction of elements by oxygen-containing organic solvents is considered to be the result of compound formation of the oxonium salt type. The ability of elements to form complex anions determines both the possibility for extraction of these elements, and their ability to be precipitated by organic bases, as well as their ability to give color reactions with colored organic cations.

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# A PHYSICO-CHEMICAL ANALYSIS OF PYRIDINE-NITROPHENOL INTERACTION

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Pyridine is found to be a good complexing agent, due to the presence of a tertiary nitrogen atom, which is an electron donor. The interaction of pyridine and phenol has been investigated by a number of authors [1,2,3], who determined that pyridine forms complexes with phenol of the composition $C_5H_5N \cdot C_6H_5OH$ and $C_5H_5N \cdot 2C_6H_5OH$. It was of interest to clarify the extent to which introduction of nitrogroups into the phenol molecule effects the nature of its reaction with pyridine. With this purpose in mind, the authors have investigated the systems of pyridine with o- and p-nitrophenols and with 2,4-dinitrophenol by the methods of fusibility, viscosity, density and electroconductivity.

Fusibility investigation was carried out by the visual-polythermal method. For density determination, a viscometer of the covered type was used. Density was determined with narrow-necked pycnometers of 4-5 ml. volume. Electroconductivity measurement was carried out by the Kolrausch method and light generator and indicating light, instead of by telephone. The investigation was carried out in a hermetically-sealed vessel with smooth platinum electrodes. Temperature of the thermostat was maintained with an accuracy of ±0.1°.

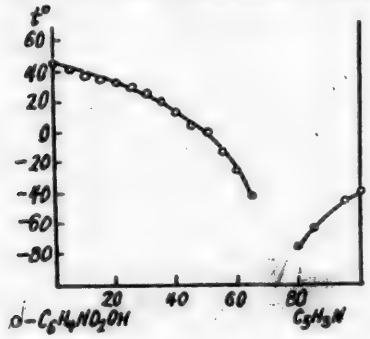


Fig. 1.

Pyridine was dried over caustic potash and fractionally distilled. The fraction with b.p. 115.5° at 760 mm pressure and $d_4^{25}$ 0.977 was distilled into ampoules and sealed. o-nitrophenol was recrystallized three times from alcohol. Melting point of the purified sample was 44.5°, $d_4^{45}$ 1.286. p-Nitrophenol, recrystallized repeatedly from water, possessed a m.p. of 113°, $d_4^{115}$ 1.286. Dinitrophenol, purified by double recrystallization from alcohol, melted at 111.3°, $d_4^{115}$ 1.44. All mixtures were calculated in mole percentages.

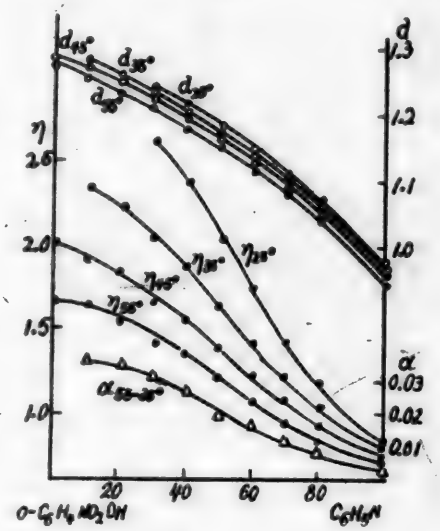


Fig. 2.

o-Nitrophenol-Pyridine System. This system was investigated by Ampola and Rimatori, by fusibility, but the authors did not arrive at any conclusions concerning interaction of the components, since they investigated only 7 mixtures in all. The present authors investigated the given system in more detail by the fusibility method. Results of the investigation are represented in Fig. 1. The mixtures in the composition range from 65 to 80 mole % of pyridine became very viscous upon cooling, but did not crystallize. All attempts to induce crystallization by the addition of seeding substances, both mixtures of similar composition, and other compounds, were unsuccessful. The mixtures solidified into transparent glassy masses at temperatures below −90°.

By viscosity Bramley [1] investigated the given system at temperatures of 30, 40, 60 and 80°. The curves obtained by him are found to be slightly convex toward the composition axis, with no outstanding points. Therefore, Bramley concluded that there is no chemical interaction between pyridine and o-nitrophenol. We have repeated investigations of the viscosity and the density of the given system at temperatures of 25, 35, 45 and 55°.

Results of the measurements are represented in Fig.2.

As can be seen from Fig. 2., the density isotherms, d, represent curves with concavity toward the composition axis, which expresses the occurrence of a certain amount of contraction in the system.

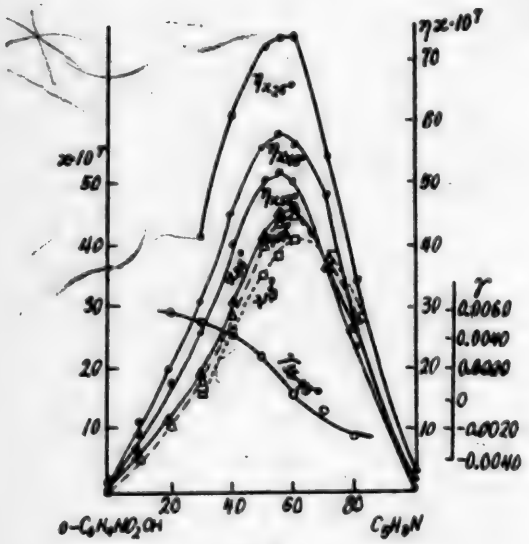


Fig. 3.

The viscosity isotherms, $\eta$, at all temperatures, are represented as S-like curves with a point of inflection at about 50% pyridine. The curve for the absolute temperature coefficient of viscosity, $\alpha$, for the temperatures range 55-35°, also represents an S-shaped curve with inflection point at about 50% pyridine. All of this permits the deduction that a compound is formed in the system, of the composition $C_5H_5N \cdot o\text{-}C_6H_4NO_2OH$. The same S-shaped viscosity isotherms were obtained by A. D. Vinogradova, A. M. Tikhomirova and N. N. Efremov for the pyridine-phenol system [3]. In that work the authors make the assumption that in the case of the nitrophenols there might be expected curves of the same type. Our investigations have confirmed the above-indicated situation. The electroconductivity of the system was studied at temperatures of 24, 45 and 55°. Results of the measurements are indicated in Fig. 3.

The isotherms of electroconductivity, $\kappa$, represent curves with considerable convexity toward the composition axis in the region of o-nitrophenol, passing through a maximum, slightly concave in the region of pyridine. The maximum electroconductivity comes at about 60 mole % pyridine. At about 70 mole % of pyridine the electroconductivity isotherms intersect at a point, after which the electroconductivity of the mixture falls with temperature increase. The curve for the relative temperature coefficient of electroconductivity, $\gamma$, has an inflection in the range of 50 mole % of pyridine.

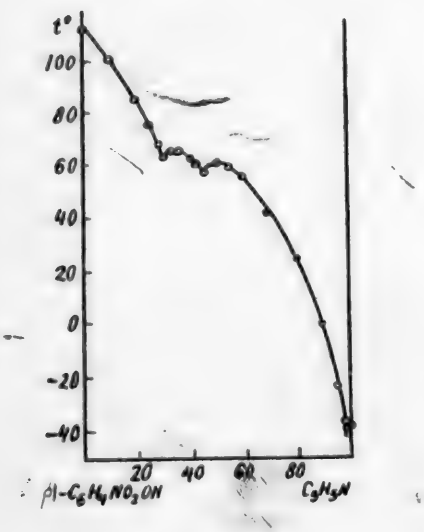


Fig. 4.

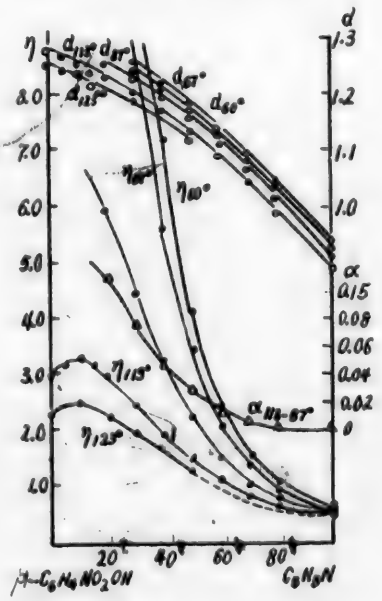


Fig. 5.

The existence of positive and negative electroconductivity coefficients for one and the same system was observed by M. I. Usanovich upon examination of the system $H_2SO_4$–$(C_2H_5)_2O$ [5] and F. I. Terpugov upon examination of the system $AsCl_3$–$(C_2H_5)_2O$ [6] and others. M. I. Usanovich [7,8] theoretically substantiated the reasons for the appearance of a negative electroconductivity temperature coefficient.

Correction of electroconductivity for viscosity, $\eta\kappa$, did not change the course of the curves, but somehow shifted the maximum closer to 50% pyridine. Electroconductivity investigation has confirmed the presence of a compound in the liquid phase of composition $C_5H_5N \cdot o\text{-}C_6H_4NO_2OH$.

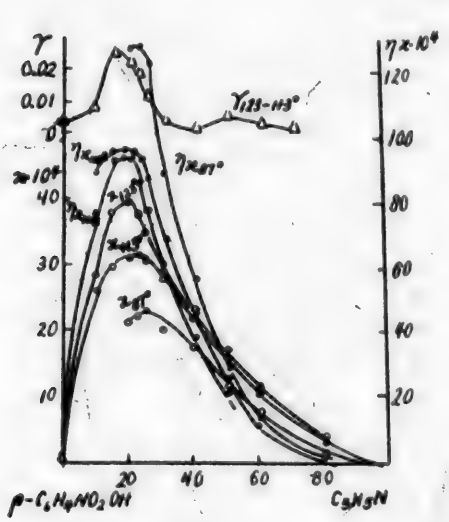


Fig. 6.

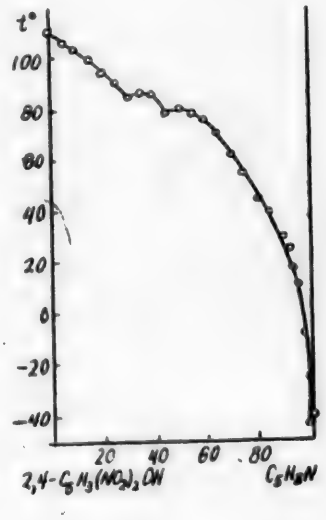


Fig. 7.

p-Nitrophenol-Pyridine System, up to the present time, has not been investigated. The results of our fusibility investigation are represented in Fig. 4.

The melting curve has two maxima, corresponding to 33.3 and to 50 mole % of pyridine, with melting points of 66 and 61.5°. This points to the formation of two compounds in the solid phase of the composition $C_5H_5N \cdot p\text{-}C_6H_4NO_2OH$ and $C_5H_5N \cdot 2p\text{-}C_6H_4NO_2OH$. The viscosity and the density of the system were determined at temperatures of 60, 67, 87, 113, 123°. Investigation results are presented in Fig. 5.

Isotherms, $\eta$, isotherms, at temperatures of 87, 113 and 123°, are represented as S-shaped curves with an inflection point of about 33.5 mole% of pyridine. It was possible only to take the 60, 67° isotherms up to 30 mole % of pyridine, but from their appearance it may be assumed that they too take the shape of S-curves.

The absolute temperature-density coefficient, $a$, curve for the temperature range 113-87° also takes an S-form with an inflection point at about 34 mole% of pyridine.

By the viscosity method the presence in the liquid phase of a combination between pyridine and p-nitrophenol of the composition $C_5H_5N \cdot 2p\text{-}C_6H_4NO_2OH$ was confirmed The electroconductivity for the system was measured at three temperatures, 87, 113 and 123°. The measurement results are presented in Fig. 6.

The isotherms for electroconductivity, $\kappa$, at all temperatures are represented by curves which are concave to the composition axis in the p-nitrophenol range, passing through a maximum, and vice versa, convex to the composition axis in the pyridine range. The electroconductivity curve form is analogous to that of the pyridine-iodine chloride system investigated by Ya. A. Fialkov and I. D. Muzyka [9]. The electroconductivity maximum at 87° comes at about 25 mole % of pyridine. With a temperature increase, the maximum is shifted toward p-nitrophenol. The curve for the relative temperature coefficient of electroconductivity has two maxima in the temperature range 123-113°, and 213-87°. Correction of electroconductivity for viscosity, $\eta\kappa$, did not change the course of the curves, and the maxima remained almost unchanged for the same compositions. The investigation of viscosity and of electroconductivity confirms the presence of one of the compounds of the composition $C_5H_5N \cdot 2p\text{-}C_6H_4NO_2OH$, which was determined by the fusibility method.

2,4-Dinitrophenol-Pyridine System was investigated by the authors for the first time. The results of fusibility investigation are presented in Fig. 7.

As with p-nitrophenol, the fusibility curve has two maxima, corresponding to the compositions 33.5 and 50 mole % of pyridine, with melting points of 86.5 and 80°. It follows that in the solid phase there are to be found two combinations of pyridine and 2,4-dinitrophenol, of the composition $C_5H_5N \cdot 2,4\text{-}C_6H_3(NO_2)_2OH$ and $C_5H_5N \cdot 2[2,4\text{-}C_6H_3(NO_2)_2OH]$. The viscosity and the density of the system were determined at temperatures of 100, 115 and 125°. Results of the measurements are presented in Fig. 8.

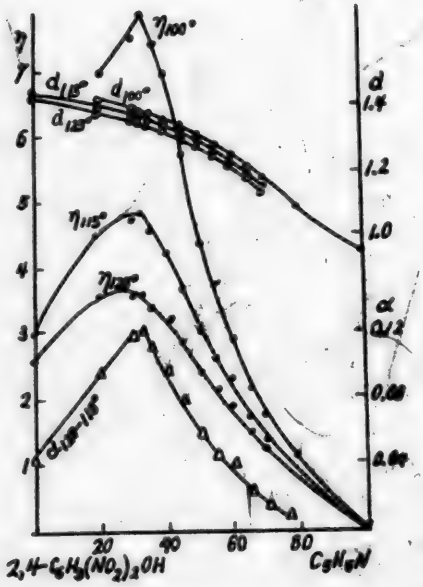


Fig. 8.

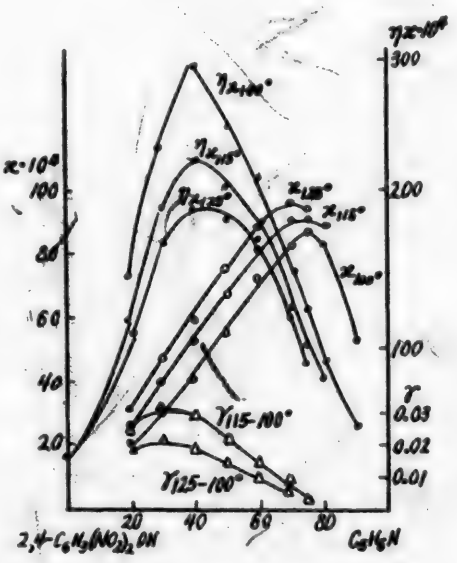


Fig. 9.

The isotherms of density, d, are represented by curves with considerable concavity to the composition axis, which attests to a greater contraction occurring in the given system than in the preceeding systems. The isotherms of viscosity, $\eta$, have a complicated form, being concave to the composition axis in the section of the curve close to 2,4-dinitrophenol, passing through a clearly-defined maximum, and convex to the composition axis in the section of curve close to pyridine. The maximum viscosity at 100° comes at 32.5 mole % of pyridine. With temperature increase it shifts slightly to the side of 2,4-dinitrophenol. The curves for the absolute temperature coefficient of viscosity, $\alpha$, at temperatures 125-115° and at 125-100° have maxima close to 33 mole % of pyridine. The electroconductivity was investigated at the same temperatures. Results of the investigations are presented in Fig. 9.

The isotherms of the electroconductivity, $\kappa$, at 100° have maxima, corresponding to 75 mole % of pyridine, shifting to the side of 2,4-dinitrophenol with temperature increase. The curves for the relative temperature coefficient of electroconductivity, $\gamma$, have a maximum corresponding to 33 mole % of pyridine. The correction of electroconductivity for viscosity, $\eta\kappa$, shifts considerably the maximum to the side of 2,4-dinitrophenol; thus at a temperature of 100° the maximum comes at 39 mole % of pyridine, with increase in temperature the maximum is shifted to the side of pyridine. According to the viscosity and electroconductivity data on the liquid pyridine-2,4-dinitrophenol system, it can be concluded that the diagrams reflect a compound of the composition $C_5H_5N \cdot 2[2,4\text{-}C_6H_3(NO_2)_2OH]$.

## SUMMARY

1. The systems formed between pyridine and each of the following: o-, p-nitrophenol and 2,4-dinitrophenol were investigated by the methods of fusibility, viscosity, density and electroconductivity.

2. The isotherms of viscosity, specific gravity, electroconductivity, reduced electroconductivity, and also the curves of temperature coefficients for the o-nitrophenol-pyridine system point to the formation in the liquid phase of a compound of the composition $C_5H_5N \cdot o\text{-}C_6H_4NO_2OH$.

3. By the method of fusibility, the formation of two compounds in the pyridine – p-nitrophenol system, of composition $C_5H_5N \cdot 2p\text{-}C_6H_4NO_2OH$ and $C_5H_5N \cdot p\text{-}C_6H_4NO_2OH$, was proven.

The isotherms of viscosity, electroconductivity, reduced electroconductivity, and also the curve of absolute temperature coefficient of viscosity, point to the existence of a compound, in the liquid phase, of the composition $C_5H_5N \cdot 2p\text{-}C_6H_4NO_2OH$.

4. The fusibility curve for the pyridine – 2,4-dinitrophenol system points to the formation of compounds in the solid phase of the composition

$C_5H_5N \cdot 2[2,4\text{-}C_6H_3(NO_2)_2OH]$ and $C_5H_5N \cdot 2,4\text{-}C_6H_3(NO_2)_2OH$.

The isotherms of viscosity, electroconductivity, reduced electroconductivity, and the curves of temperature coefficients, confirm the presence of a compound in the liquid phase, of the composition $C_5H_5N \cdot 2[2,4\text{-}C_6H_3(NO_2)_2OH]$.

5. Introduction of the nitro group into phenol promotes the formation of a chemical interaction with pyridine if the nitro group is situated in the p-position; the presence of the nitro group in the o-position inhibits interaction with pyridine, due to the o-effect action. Introduction of a second nitro group into the phenol molecule augments interaction with pyridine.

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# SOME COMPOUNDS OF PYRIDINE WITH CUPRIC CHLORIDE

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Complex compounds of pyridine with salts of divalent copper have been the subject of investigation by many scientists. However, the number of compounds obtained remains comparatively small. Thus, for example, cupric chloride forms compounds of $CuCl_2 \cdot 2Pyr$, which give with hydrochloric acid a new product of the composition $CuCl_2 \cdot 2Pyr \cdot 2HCl$, crystallizing in the form of yellow prisms [1]. According to the data of Spero and Metyu [2], in the pyridine-cupric chloride system there come out three compounds in the solid phase: $CuCl_2 \cdot 2Pyr$, $2CuCl_2 \cdot 3Pyr$ and $CuCl_2 \cdot 6Pyr$. There are also indications of the existence of the compound $2CuCl_2 \cdot 3Pyr$ [3].

As the authors' experiments have shown, cupric chloride forms with pyridine a series of compounds, which have not been described up to the present, as far as is known through the literature, which is accessible to the authors. Upon interaction of cupric chloride with pyridine, in absolute alcohol or in dry acetone, the authors have obtained a compound of the composition $CuCl_2 \cdot Pyr$. For this purpose anhydrous cupric chloride and pyridine were taken in strictly equimolecular quantities. At first, upon addition of pyridine to a solution of cupric chloride in one of the indicated solvents, there is formed a blue compound, of the composition $CuCl_2 \cdot 2Pyr$, which subsequently converts into the compound $CuCl_2 \cdot Pyr$. Such a transformation occurs very slowly at room temperature. The reaction is accelerated considerably upon boiling in a flask equipped with reflux. The blue color then changes to grey. In acetone the reaction is complete after 2-3 hours, i.e., somewhat more rapidly than in absolute alcohol.

0.0982 g substance: 0.1315 g AgCl. 0.1166 g substance: 0.1553 g AgCl. 0.0960 g substance: 0.0289 g Cu. 0.1488 g substance: 0.0441 g Cu. 0.2721 g substance: 17.5 ml $N_2$ (23°, 716.5 mm); 0.2369 g substance: 14.3 ml $N_2$ (24°, 717.5 mm). Found %: Cl 33.04, 32.95; Cu 30.11, 29.64; N 6.79, 6.37. $CuCl_2 \cdot Pyr$. Calculated %: Cl 29.77; Cu 33.14; N 6.56.

The compound obtained interacts with mineral acids. With hydrochloric acid there is formed an equimolecular mixture of two compounds: $CuCl_2 \cdot 2Pyr \cdot 2HCl$, crystallizing in the form of yellow prisms, and $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$ — in the form of dark-brown. This reaction can likewise occur in the vapors of hydrochloric acid, but does not occur in an atmosphere of dry hydrogen chloride.

The reaction carried out in vapors of hydrochloric acid gave the following results: 0.2569 g and 0.3879 g of $CuCl_2 \cdot Pyr$ increased, respectively, in weight by 0.0523 and 0.0822 g. Assuming an equimolecular mixture is formed, the calculated increase in weight is equal to 0.0547 and 0.0826 g. Analysis of the reaction products likewise confirms the accuracy of such a conclusion.

0.4701 g mixture: 0.7831 g AgCl. 0.1117 g mixture: 0.0277 g Cu. Found %: Cl 41.17; Cu 24.80. Calculated %: Cl 41.07; Cu 24.54.

$CuCl_2 \cdot Pyr$ does not dissolve in organic solvents. It is decomposed into $CuCl_2 \cdot 2Pyr$ and $CuCl_2$ by water. Upon heating above 200° the compound gradually loses pyridine, transforming into anhydrous cuprous chloride. The decomposition temperature is 247-249°.

The compound of composition $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$ is obtained from an aqueous solution containing excess hydrochloric acid with exact stoichiometric quantities of cupric chloride and pyridine. If to the stoichiometric quantities of cupric chloride and pyridine there is added the exact calculated quantity of hydrochloric acid essential for formation of the indicated compound, from the resulting dark-green solution there will precipitate $CuCl_2 \cdot Pyr$ in the form of grey flakes. The addition of excess hydrochloric acid leads to solution of the dark-grey precipitate of $CuCl_2 \cdot Pyr$, and consequent concentration of the solution by boiling leads to precipitation of dark-brown crystals, of the composition $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$. The compound obtained can be purified by recrystallization from aqueous solution.

0.0405 g substance: 0.0693 g AgCl. 0.0879 g substance: 0.1505 g AgCl. 0.2047 g substance: 0.0559 g Cu; 0.2258 g substance: 0.0643 g Cu. 0.3524 g substance: 14.4 ml $N_2$ (24°, 732 mm). 0.3425 g substance: 12.2 ml $N_2$ (20.5°, 723 mm). 0.2052 g substance: 0.0179 g $H_2O$; 0.3432 g substance: 0.0280 g $H_2O$. Found %: Cl 42.30, 42.33; Cu 28.56, 28.35; N 4.32, 4.15; $H_2O$ 8.72, 8.16. $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$. Calculated %: Cl 42.27; Cu 28.44; N 4.18; $H_2O$ 8.15.

The compound obtained decomposes when dissolved in alcohol, with the formation of $CuCl_2 \cdot 2Pyr$, and in acetone with $CuCl_2 \cdot 2Pyr \cdot 2HCl$. It is insoluble in benzene, carbon tetrachloride, and similar solvents. It melts with decomposition at 194-195°.

The electroconductivity of the aqueous solution at 25° indicates that this compound dissociates into its component ions:

| $\nu$ | 125 | 250 | 500 | 1000 | 2000 |
|---|---|---|---|---|---|
| $\mu$ | 830.7 | 881.0 | 923.0 | 946.6 | 961.6 |

In the air $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$ gradually loses water and hydrogen chloride, transforming into the compound $3CuCl_2 \cdot 2Pyr$, a light-green powder. The compound $3CuCl_2 \cdot 2Pyr$ is not formed directly from cuprous chloride and pyridine. There results thermal decomposition of $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$.

0.0431 g substance: 0.0663 g AgCl. 0.1073 g substance: 0.1657 g AgCl. 0.2062 g substance: 0.0703 g Cu. 0.1212 g substance: 0.0413 g Cu. 0.4239 g substance: 18.2 ml $N_2$ (21°, 728.5 mm); 0.4912 g substance: 23.4 ml $N_2$ (22.5°, 723.5). Found %: Cl 38.18, 38.06; Cu 34.17, 34.08; N 4.93, 5.09. $3CuCl_2 \cdot 2Pyr$. Calculated %: Cl 37.88; Cu 33.95; N 4.98.

In water $3CuCl_2 \cdot 2Pyr$ decomposes with the formation of $CuCl_2 \cdot 2Pyr$. It does not dissolve in organic solvents. It is soluble in acids. With hydrochloric acid it gives a compound $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$. It is stable in air. Upon heating above 100°, it decomposes with the formation of cupric chloride. It melts with decomposition at 272-273°.

The compound with six molecules of pyridine $CuCl_2 \cdot 6Pyr$ was obtained by the action of considerable pyridine excess upon anhydrous cupric chloride. At first there is formed the compound $CuCl_2 \cdot 2Pyr$, and subsequently, after about ten days, if the temperature does not exceed 12-15°, there results a compound of the composition $CuCl_2 \cdot 6Pyr$, dark blue in color. Upon cooling to −10°, and lower, the formation of $CuCl_2 \cdot 6Pyr$ occurs much more rapidly. The compound is stable in pyridine solution at a temperature not over 15°, while according to the literature data it is stable only at −10°. It decomposes in the air with the formation of $CuCl_2 \cdot 2Pyr$.

0.4508 g $CuCl_2 \cdot 6Pyr$ loss in weight 0.2342 g. For a loss of 4 pyridine molecules, the calculated weight loss is 0.2343 g.

0.1003 g substance: 0.0456 g AgCl. 0.4204 g substance: 0.1988 g AgCl. 0.4508 g substance: 0.0450 g Cu. 0.2550 g substance: 0.0261 g Cu. Found %: Cl 11.25, 11.43; Cu 9.98, 10.24. $CuCl_2 \cdot 6Pyr$. Calculated %: Cl 11.65; Cu 10.44.

## SUMMARY


1. Upon interaction of cupric chloride with pyridine in absolute alcohol or dry acetone, there is formed a compound of the composition $CuCl_2 \cdot Pyr$.

2. Upon interaction of stoichiometric quantities of cupric chloride and pyridine in hydrochloric acid solutions, there is formed a compound of the composition $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$.

3. It was demonstrated that upon thermal decomposition of the compound $3CuCl_2 \cdot 2Pyr \cdot 2HCl \cdot 2H_2O$ there is formed the compound $3CuCl_2 \cdot 2Pyr$.

4. The compound $CuCl_2 \cdot 6Pyr$, known in the literature, is stable at temperatures not exceeding 15°.


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# INVESTIGATIONS IN THE FIELD OF REDOX TRANSFORMATIONS

## I. POLAROGRAPHIC INVESTIGATION OF 1-CHLOROBUTANONE-2, 3-CHLOROBUTANONE-2, PROPIONYLCARBINOL AND METHYLACETYLCARBINOL

M. I. Bobrova and N. S. Tikhomirova

The works of Winkel and Proske are devoted to the reduction of hydroxycarbonyl compounds, and in particular, to methylacetylcarbinol (acetoin) in 0.1 N $NH_4Cl$, at the dropping mercury electrode.

The authors determined the so-called "decomposition potential". For methylacetylcarbinol it was found to be equal to −1.7 V at a concentration of $10^{-3}$ M/liter.

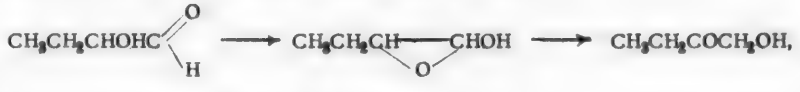
Tachi [3] determined the decomposition potential of methylacetylcarbinol according to the tangential method in acid medium and found it equal to −1.14 V.

The authors mentioned limited themselves to the determination of redox potentials at one given concentration. They did not determine the value for the polarographic constant nor the electron discharge upon reduction of 1 mole of substance.

M. I. Bobrova and P. N. Sokolov [4] have made polarograms of 1-chlorobutanone-2 and 3-chlorobutanone-2 in media of 0.01 N HCl, 0.01 N KCl and in 80% ethanol for the sole purpose of determining half-wave potentials.

S. N. Danilov, E. D. Venus-Danilova and V. F. Kazimirova have demonstrated in their multiple investigations that hydroxyaldehydes can give isomeric secondary keto-alcohols in acid or alkaline medium.

Diphenylglycolic [5], benzylglycolic [6], alpha-hydroxyisobutyric [7], dicyclohexylglycolic [8], alpha-hydroxyhexahydrobenzoic [9], alpha-hydroxybutyric [10] and alpha-hydroxyenanthic [11] aldehydes were isomerized into the corresponding secondary ketoalcohols. In no case was a primary ketoalcohol obtained whose formation was to be expected using the alcohol-oxidizing schemes of Favorsky. Thus, for instance, the formation of propionylcarbinol from α-hydroxybutyric aldehyde would be expected



but in practice methylacetylcarbinol was obtained.

There arose the question of whether or not propionylcarbinol is the intermediate product in the isomerization of α-hydroxybutyric aldehyde to methylacetylcarbinol For this purpose it was necessary to verify the possibility of transformation of propionylcarbinol into methylacetylcarbinol under analogous conditions. Such experiments have been carried out by S. N. Danilov and N. S. Tikhomirova, starting with the same ketoalcohol and its corresponding chloroketone of 1-chlorobutanone-2 [12]. For study of this problem we have turned to the method of polarography which, it seemed, would give the opportunity of: 1) determining each of the named substances individually or in their mixture resulting from reaction; 2) allowing conclusions about the transformation possibility of the primary ketoalcohol to the secondary from the obtained half-wave potentials of these substances, of their polarographic constants, and of the electron consumption upon reduction of 1 mole of the substance.

Kern [13] made use of certain hydroxycarbonyl compounds in the role of polymerization initiators. We assume that the polarographic method can give indication as to which one of the ketoalcohols will prove to be more active under the conditions of polymerization.

### EXPERIMENTAL

The chloroketones and ketoalcohols were synthesized as described earlier [12], and possessed the constants indicated in Table 1.

TABLE 1

| Substance | Boiling point | $d_4^{20}$ | $n_a^{20}$ | $n_D^{20}$ | $MR_D$ found | $MR_D$ calculated |
|---|---|---|---|---|---|---|
| 1-Chlorobutanone-2 | 137-138° | 1.0850 | 1.4311 | – | 25.42 | 25.42 |
| 3-Chlorobutanone-2 | 116-117 | 1.05705 | 1.4210 | – | 25.55 | 25.42 |
| Propionylcarbinol | 78° (60 mm) | 1.0264 | – | 1.4248 | 22.04 | 22.21 |
| | 54 (18 mm) | | | 1.4248 | | |
| Methylacetylcarbinol | 38 (12 mm) | 1.0101 | – | 1.4200 | 22.04 | 22.21 |
| | 40 (13 mm) | | | 1.4197 | | |
| Methylacetylcarbinol dimer • | – | – | – | – | – | – |

Methylacetylcarbinol dimer was obtained after double distillation in vacuo of the ketoalcohol, and had a melting point as indicated in the literature [14].

The polarography was carried out in a Gorky ("Etalon" factory) polarograph M-7, with a mirror galvanometer, whose sensitivity on a scale length of 100 centimeters is equal to 175 mm/μA. For the work, shunts were used from 1/5 to 1/200 of the current sensitivity.

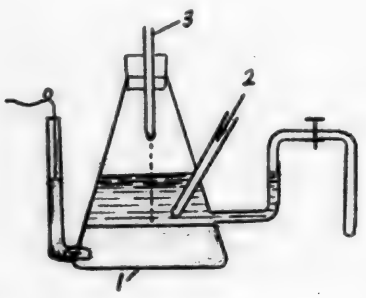



Fig. 1. Electrolyzer
1) mercury anode; 2) tube for hydrogen conduction; 3) capillary.

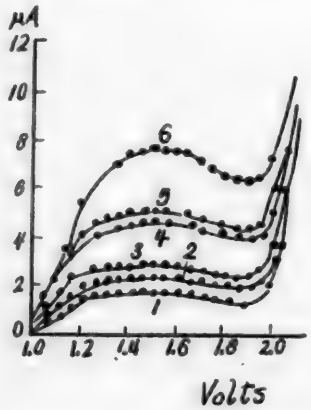



Fig. 2. Polarograms of 1-chlorobutanone-2 in 0.1 N solution of $NH_4Cl$ (20 ml). Weighed portions (g): 1) 0.0112, 2) 0.0116, 3) 0.0204, 4) 0.0240, 5) 0.0282, 6) 0.0410.

The polarography was conducted in an electrolyzer, pictured in Fig. 1. On the left is located the current outlet from the anode, and on the right a tube with stopcock, which is utilized for measuring the potential of the bottom and the pH of the solution under study, and likewise a tube for conducting hydrogen for the purpose of removing dissolved oxygen from the solution.

Capillary characteristic: mass of the mercury drop = 0.0025 g, dropping period = 3.75 sec. Resistance of the solutions studied, $R \simeq 3000$ ohms. Primary and secondary chloroketones were studied in the concentration range from $1 \times 10^{-3}$ to $2.8 \times 10^{-2}$ moles/liter, the propionylcarbinol from $1.2 \times 10^{-2}$ to $3 \times 10^{-2}$ moles/liter, and the methylacetylcarbinol from $5 \times 10^{-3}$ to $1.8 \times 10^{-2}$ moles/liter.

As the phonic background, the electrolyte mixture employed was 0.1 N KCl, 0.1 N $NH_4Cl$ and borate buffer with pH = 10.0. All half-wave potential values ($E_{1/2}$) are referred to the saturated calomel electrode potential with correction for $\underline{iR}$.

The polarographic results for 1-chlorobutanone-2 in 0.1 N $NH_4Cl$ solution are presented in Fig. 2.** From examination of the polarograms, it is apparent that upon reduction of 1-chlorobutanone-2 at the dropping mercury electrode in 0.1 N $NH_4Cl$, there is only one polarographic wave. The half-wave ($E_{1/2}$) potential found graphically at $\underline{i_d/2}$ with a correction for $\underline{iR}$ is equal to −1.104V. The value $E_{1/2}$ found at

$$\log \frac{i}{i_d - i} = 0,$$ is −1.09. The polarographic constant ($i_d/C$) i.e. the diffusion current with regard to unit concentration = 1614 μA/g. The dependence of $\log \frac{i}{i_d - i}$ upon E is presented in Fig. 3. The number of electrons participating in the reduction of

• M.p. 95.5°.

** On all polarograms the diffusion current values are quoted 10 times smaller than the actual

1 mole of the substance ($a$) [15] (which is apparent in the case of a non-reversible reduction) is determined from the wave equation by the tangent of the inclination angle of the straight line $\log \frac{i}{i_d - i}$ to E, namely

at $t = 15°$

$$E = E_{1/2} - \frac{0.057}{a} \log \frac{i}{i_d - i};$$

from which

$$a = 0.057 \frac{\Delta \log \frac{i}{i_d - i}}{\Delta E} = 0.513.$$

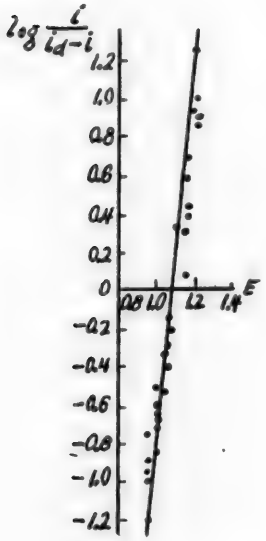



Fig. 3. Relation of $\log \frac{i}{i_d - i}$ to E for 1-chlorobutanone-2 in 0.1 N $NH_4Cl$.

The polarographic results for 1-chlorobutanone-2 in borate buffer solution at pH = 10.0 are presented in Fig.4. From examination of the polarograms, it is apparent that the reduction of 1-chlorobutanone-2 in buffer solution is likewise accompanied by the formation of one polarographic wave with $E_{1/2} = -1.087$ V, by the graphic method of determination of potential, i.e. at $i_d/2$.

In the instance $\log \frac{i}{i_d - i} = 0$, $E_{1/2} = -1.110$ V.

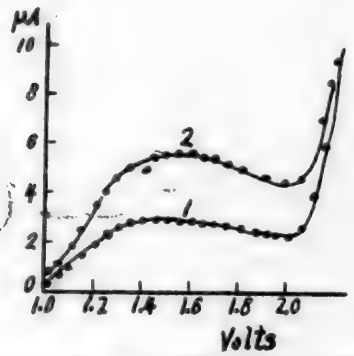



Fig. 4. Polarograms for 1-chlorobutanone-2 in buffer solution at pH = 10.0 (20 ml). Weighed portions (g): 1) 0.0130, 2) 0.0268.

The polarographic constant ($i_d/C$) for 1-chlorobutanone-2 at pH = 10.0 is equal to 1720 μA/g. The relation between $\log \frac{i}{i_d - i}$ and E is presented in Fig. 5.

The polarographic results for 3-chlorobutanone-2 in 0.1 N $NH_4Cl$ are presented in Fig.6. It is apparent from the polarograms that the half-wave potential of 3-chlorobutanone-2 in 0.1 N $NH_4Cl$ = 1.044 V. The polarographic constant $i_d/C$ = 1075 μA/g. The relation $\log \frac{i}{i_d - i}$ to E is presented in Fig. 7. The value of $a$ = 0.353.

The polarographic results for 3-chlorobutanone-2 in borate buffer solution at pH = 10.0 are presented in Fig 8. It is apparent from the polarograms that upon reduction of 3-chlorobutanone-2 at pH = 10.0, there is formed a wave whose half-wave potential at $i_d/2 = -1.049$ V, and at $\log \frac{i}{i_d - i} = 0$, the value for $E_{1/2} = -1.080$ V. The polarographic constant $i_d/C$ = 1071 μA/g. The relation of $\log \frac{i}{i_d - i}$ to E is represented in Fig. 9. The value for $a$ = 0.285.

The polarographic results for propionylcarbinol in 0.1 N KCl are represented in Fig. 11. It is apparent from examination of the polarograms that upon reduction of propionylcarbinol in 0.1 N KCl, there occurs one wave from which $E_{1/2}$ found at $i_d/2$ is equal to −1.772 V, and at $\log \frac{i}{i_d - i} = 0$ is equal to −1.81 V. The polarographic

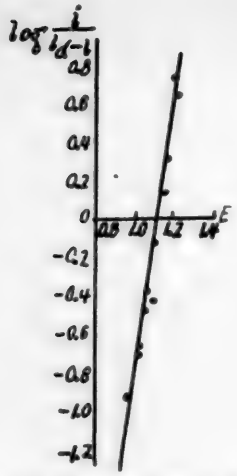


Fig. 5. Relation of $\log \frac{i}{i_d - i}$ to E for 1-chlorobutanone-2 in buffer solution at pH = 10.0

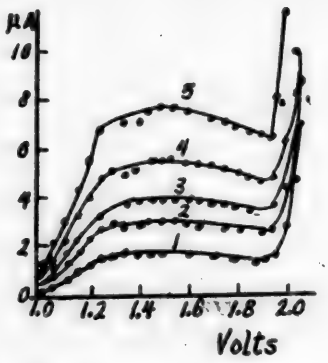



Fig. 6. Polarograms for 3-chlorobutanone-2 in 0.1 N $NH_4Cl$ (20 ml). Weighed portions (g): 1) 0.0124, 2) 0.0234, 3) 0.0312, 4) 0.0413, 5) 0.0601.

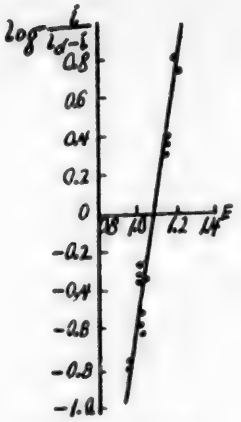


Fig. 7. Relation of $\log \frac{i}{i_d - i}$ to E for 3-chlorobutanone-2 in 0.1 N $NH_4Cl$.

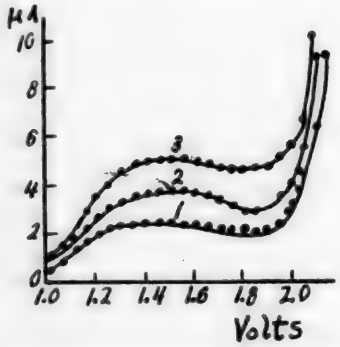



Fig. 8. Polarograms of 3-chlorobutanone-2 in buffer solution at pH = 10.0 (20 ml). Weighed portions (g): 1) 0.0210, 2) 0.0306, 3) 0.0426.

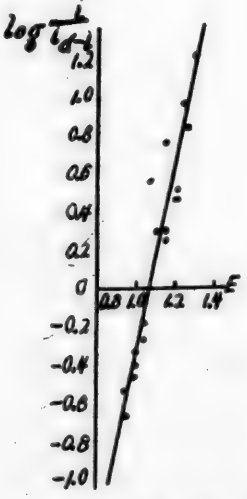


Fig. 9. Relation of $\log \frac{i}{i_d - i}$ to E for 3-chlorobutanone-2 in buffer solution at pH = 10.0

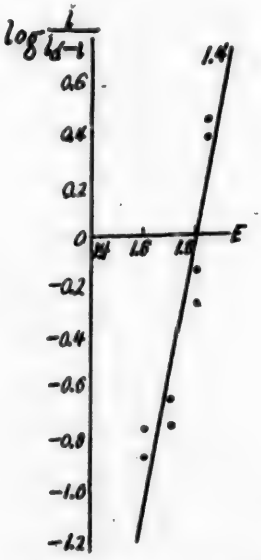


Fig. 10. Relation of $\log \frac{i}{i_d - i}$ to E for propionylcarbinol in 0.1 N KCl.

constant ($i_d/C$) for propionylcarbinol was found to be equal to 919 μA/g. The relation of $\log \frac{i}{i_d - i}$ to E is represented in Fig. 10. The value for $\alpha = 0.29$.

The polarography of propionylcarbinol in borate buffer solution at pH = 10.0 gave no waves. This indicates that propionylcarbinol at pH = 10.0 is not reduced. The polarographic results for methylacetylcarbinol in 0.1 N $NH_4Cl$ are represented in Table 12. From examination of the polarograms it is apparent that upon reduction of methylacetylcarbinol in 0.1 N $NH_4Cl$ there occurs one polarographic wave, the half-wave value for which ($E_{1/2}$) at $i_d/2$ is equal to −1.684 V, and upon $\log \frac{i}{i_d - i} = 0$ is equal to −1.82 V. The polarographic constant $i_d/C$ = 5097 μA/g. The relation of $\log \frac{i}{i_d - i}$ to E is represented in Fig. 13. The value of $\alpha = 0.47$.

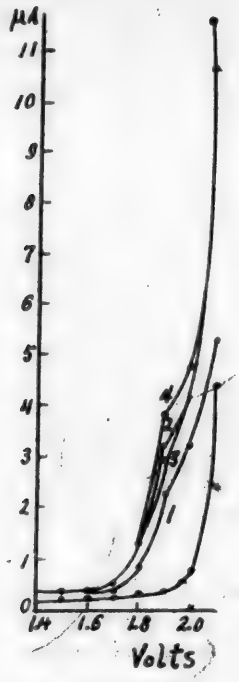



Fig. 11. Polarograms for propionylcarbinol in 0.1 N KCl (20 ml). Weighed portions(g): 1) 0.0214, 2) 0.0334, 3) 0.0334, 4) 0.0401.

Fig. 12. Polarograms for methylacetylcarbinol in 0.1 N $NH_4Cl$ (20 ml). Weighed portions(g) 1) 0.0088, 2) 0.0090, 3) 0.0148, 4) 0.0174, 5) 0.0207, 6) 0.0252, 7) 0.0304, 8) 0,0314, 9) 0.426, 10) ground.

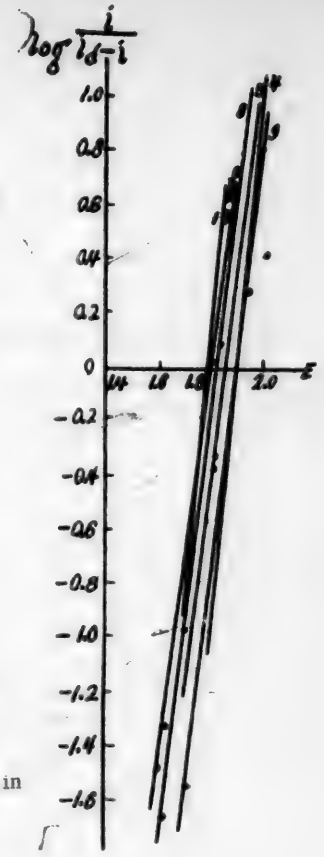



Fig. 13. Relation of $\log \frac{i}{i_d - i}$ to E for methylacetylcarbinol in 0.1 N $NH_4Cl$.

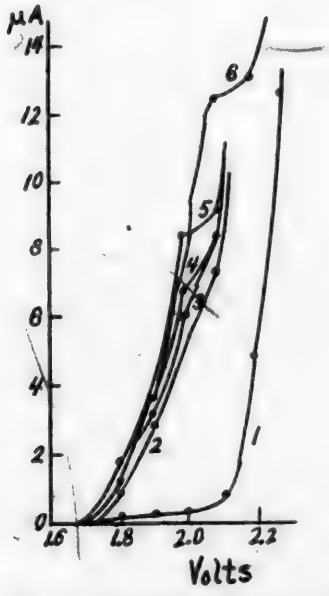



Fig. 14. Polarograms for methylacetylcarbinol in buffer solutions at pH = 10.0 (20 ml). Weighed portions (g): 1) ground, 2) 0.0250, 3) 0.0257, 4) 0.0334, 5) 0.0426, 6) 0.0593.

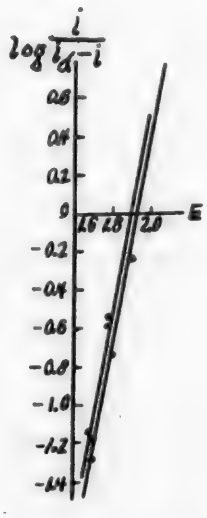



Fig. 15. Relation of $\log \frac{i}{i_d - i}$ to E for methylacetylcarbinol at pH = 10.0.

The polarographic results for methylacetylcarbinol in borate buffer solution at pH = 10.0 are presented in Fig. 14.

The relation $\log \frac{i}{i_d - i}$ to E for methylacetylcarbinol at pH = 10.0 is represented in Fig. 15. The value for $\alpha$ = 0.32.

The relation of $E_{1/2}$ to concentration for propionylcarbinol and methylacetylcarbinol is represented in Fig. 16.

The reduction of methylacetylcarbinol dimer at the dropping mercury cathode takes place analogously to

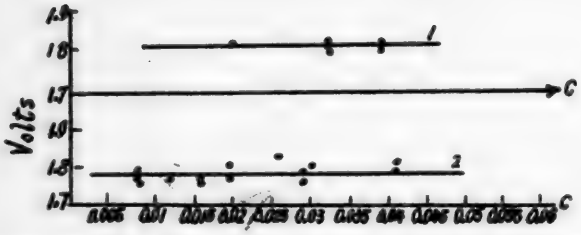



Fig. 16. Relation of $E_{1/2}$ to concentration for propionylcarbinol and methylacetylcarbinol. 1) propionylcarbinol, 2) methylacetylcarbinol.

the reduction of methylacetylcarbinol. The half-wave potential and the polarographic constant for the dimer have values close to that of methylacetylcarbinol.

With polarography of methylacetylcarbinol monomer and dimer, maxima occurred in the polarograms in a series of instances.

Evaluation of Results

A complete summarization of the data on the polarographic investigation carried out by the authors is represented in Table 2. The results of polarographic measurements for 1-chlorobutanone-2 and 3-chlorobutanone-2 indicate that primary and secondary chloroketones are simultaneously reduced at the dropping mercury electrode, since their half-waves ($E_{1/2}$) potentials are very close to each other (−1.066 and −1.077 V). Therefore, their qualitative analysis in binary mixtures is impossible, since there will occur only one common wave on the polarogram of such a mixture, the height of which should be the sum of the heights of the separate chloroketone waves composing the mixture.

The value for the diffusion current, as related to the unit mass of reducible substance, i.e. $i_d/C$, differs quite markedly (1614 $\mu A/g$ and 1075 $\mu A/g$). The polarographic constant, $i_d/C$ for the primary chloroketone, both in $NH_4Cl$ and in borate buffer at pH = 10.0, exceeds by about 1.5 times the polarographic constant for the secondary chloroketone, and the apparent electron consumption for one mole of reducible substance ($\alpha$) is greater by the same number for primary chloroketones as over and above that for the secondary chloroketone. The values of the polarographic constant for primary chloroketone in solutions of ammonium chloride, and in borate buffer, at pH = 10.0. differ very little in magnitude. The same can be said for the polarographic constant of secondary chloroketone. It does not change in value in going from ammonium chloride solution to borate buffer at pH = 10.0. Thus, transition from a weak acid medium to an alkaline medium did not show any effect on the character of the chloroketone reductions.

As a result of the data obtained for the chloroketones investigated, a satisfactory relation was found between the diffusion current value, or in other words the wave height, and the concentration of chloroketones. Thus the qualitative determination of the individual chloroketones was made possible.

The electron consumption for 1 mole of substance was expressed as a fractional number in all cases. This indicates that reduction of 1-chlorobutanone-2, 3-chlorobutanone-2, propionylcarbinol and methylacetylcarbinol at the dropping mercury electrode proceeds irreversibly.

Comparing experimental data for methylacetylcarbinol with the data of Winkel and Proske [1,2], the authors have noted that if one and the same method is employed for determination of the reduction potential, there will be good agreement of results. The reduction potential found by the authors, using Winkel and Proske's method, is equal to −1.69 V, which Winkel and Proske found to be equal to −1.70 V. The data obtained by Tachi [3] are considerably more positive than those of the authors and of Winkel and Proske, even after discounting the pH difference for the media and the method for the determination of the value.

From a comparison of the polarographic data of methylacetylcarbinol with that of propionylcarbinol, it follows that the half-wave potentials of these substances are very close to one another (−1.743 V, −1.791 V), which indicates that the display of their reactive capacities at the dropping mercury cathode proceeds under the same conditions; in other words, the reduction of methylacetylcarbinol and propionylcarbinol in mixtures of one with the other, start at one and the same potential drop, i.e., simultaneously. Polarograms for such a mixture should have one wave common for the methylacetylcarbinol and propionylcarbinol, the height of which is equal to the sum of the wave heights of these two components.

It follows from the data obtained, that in the case of methylacetylcarbinol and propionylcarbinol the

TABLE 2

| Expt. nos. in order | Name of substance and the phonic (background) electrolyte (20 ml) | Weighed portion (g) | Diffusion current $i_d$ (in μA) | Polarographic constant $i_d/C$ $\left(\text{in } \frac{\mu A}{g}\right)$ | Half-wave potential ($E_{1/2}$) with respect to the saturated calomel electrode (in volts) | | | Average value for $E_{1/2}$ (in volts) | Average value for $i_d/C$ $\left(\text{in } \frac{\mu A}{g}\right)$ | Electron discharge for one mole of the substance α |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | at $\frac{i_d}{2}$ | with correction for iR | at $\log\frac{i}{i_d - i} = 0$ | | | |
| 1 | 1-chlorobutanone-2 in 0.1 N $NH_4Cl$ | 0.0112 | 13.0 | – | – | – | – | | | |
| 2 | | 0.0116 | 19.9 | 1715 | −1.100 | −1.070 | −1.09 | | | |
| 3 | | 0.0204 | 33.3 | 1636 | −1.112 | −1.055 | −1.09 | | | |
| 4 | | 0.0240 | 39.4 | 1642 | −1.095 | −1.036 | −1.09 | −1.066 | 1614 | 0.513 |
| 5 | | 0.0282 | 43.4 | 1540 | −1.102 | −1.037 | −1.09 | | | |
| 6 | | 0.0410 | 63.5 | 1539 | −1.140 | −1.045 | −1.09 | | | |
| 1 | 1-chlorobutanone-2 in buffer solution at pH = 10.0. | 0.0130 | 22.9 | 1761 | −1.140 | −1.106 | −1.11 | −1.098 | 1720 | 0.399 |
| 2 | | 0.0268 | 45.0 | 1680 | −1.135 | −1.067 | −1.11 | | | |
| 1 | 3-chlorobutanone-2 in 0.1 N $NH_4Cl$ | 0.0124 | 13.7 | 1105 | −1.120 | −1.099 | −1.11 | | | |
| 2 | | 0.0234 | 25.5 | 1089 | −1.123 | −1.087 | −1.11 | | | |
| 3 | | 0.0312 | 33.2 | 1064 | −1.119 | −1.069 | −1.11 | −1.077 | 1075 | 0.353 |
| 4 | | 0.0431 | 45.2 | 1048 | −1.080 | −1.012 | −1.11 | | | |
| 5 | | 0.0601 | 64.3 | 1070 | −1.120 | −1.024 | −1.11 | | | |
| 1 | 3-chlorobutanone-2 in buffer solution at pH = 10.0. | 0.0210 | 20.9 | 995 | −1.075 | −1.044 | −1.08 | | | |
| 2 | | 0.0306 | 34.6 | 1130 | −1.100 | −1.048 | −1.08 | −1.064 | 1071 | 0.285 |
| 3 | | 0.0426 | 46.2 | 1089 | −1.125 | −1.056 | −1.08 | | | |
| 1 | Propionylcarbinol in 0.1 N KCl | 0.0214 | 19.6 | 925 | −1.81 | −1.780 | −1.81 | | | |
| 2 | | 0.0334 | 31.2 | 934 | −1.82 | −1.770 | −1.81 | | | |
| 3 | | 0.0334 | 29.3 | 876 | −1.82 | −1.770 | −1.81 | −1.791 | 919 | 0.290 |
| 4 | | 0.0401 | 37.6 | 939 | −1.825 | −1.769 | −1.80 | | | |
| 1 | Methylacetylcarbinol in 0.1 N $NH_4Cl$ | 0.0088 | 39.8 | 4391 | 1.80 | −1.740 | −1.79 | | | |
| 2 | | 0.0090 | 48.0 | 5333 | −1.80 | −1.728 | −1.77 | | | |
| 3 | | 0.0148 | 86.8 | 5865 | −1.80 | −1.670 | −1.79 | | | |
| 4 | | 0.0174 | 98.4 | 5655 | −1.80 | −1.652 | −1.79 | −1.743 | 5097 | 0.47 |
| 5 | | 0.0207 | 114.0 | 5507 | −1.85 | −1.679 | −1.87 | | | |
| 6 | | 0.0252 | 103.6 | 4118 | −1.87 | −1.715 | −1.82 | | | |
| 7 | | 0.0304 | 148.0 | 4869 | −1.85 | −1.628 | −1.84 | | | |
| 1 | Methylacetylcarbinol in buffer solution at pH = 10.0 | 0.0250 | 52.8 | 2112 | −1.89 | −1.811 | 1.90 | | | |
| 2 | | 0.0257 | 61.4 | 2236 | −1.89 | −1.795 | – | | | |
| 3 | | 0.0334 | 67.2 | 1892 | −1.89 | −1.789 | – | −1.853 | 2112 | 0.320 |
| 4 | | 0.0426 | 84.8 | 1989 | −1.94 | −1.813 | 1.92 | | | |
| 5 | | 0.0593 | 128.6 | 2339 | −1.97 | −1.777 | – | | | |

existence of a satisfactory relation between the height of the wave and the concentration was likewise found. Consequently, there exists the possibility of quantitative analysis for the two ketoalcohols, separately, which are present.

The polarographic constants for these two substances differ considerably from one another, namely $i_d/C$ for methylacetylcarbinol is approximately 5 times greater than that for propionylcarbinol under analogous conditions (5097 and 919 μA/g). The apparent consumption of electrons for 1 mole of reducible substance for methylacetylcarbinol is likewise 1.62 times higher than that for propionylcarbinol. With an increase in pH, the value for the polarographic constant drops for methylacetylcarbinol, because its capacity for reduction in alkaline medium is less.

The effect of pH of the medium is apparent for ketoalcohol reduction, which was not observed for the chloroketone reductions. Propionylcarbinol is not reduced at pH = 10, and methylacetylcarbinol reduction proceeds less readily than in weak acid medium (Table 2). This is explained by the fact that alcoholic groups are easily oxidized in alkaline medium.

From a comparison of the polarographic data of propionylcarbinol and methylacetylcarbinol with the polarographic data of their corresponding chloroderivatives, i.e., 1-chlorobutanone-2 and 3-chlorobutanone-2, it follows that the polarographic constant ($i_d/C$) for the primary ketoalcohol is smaller than that of the secondary, while at the same time the polarographic constant for its corresponding primary chloroketone is larger, on the other hand, than for the secondary chloroketone. The apparent electron consumption for the primary chloroketone likewise exceeds the value, $\alpha$, of the secondary chloroketone, for both polarography in 0.1 N $NH_4Cl$ solution, and in borate buffer at pH = 10.0 by about 1.5 times. But for the corresponding primary ketoalcohol the value, $\alpha$, is smaller than the value, $\alpha$, for the secondary ketoalcohol, likewise by about 1.5 times. Thus, the polarographic behavior of the primary ketoalcohol, in comparison with the secondary, is directly opposite to that which takes place under the given conditions for the corresponding primary chloroketones in comparison with the secondary.

The polarographic data obtained are in agreement with the experimental data of S. N. Danilov and N. S. Tikhomirova [12], according to which 1-chlorobutanone-2 transforms, under the conditions of alkaline medium, not into the corresponding, but into the isomeric ketoalcohol, namely in the methylacetylcarbinol, at the same time that propionylcarbinol, under these conditions, does not undergo hydroxyketone transformation into the isomeric ketoalcohol. It is possible, in the case of chloroketone, that transformation proceeds in the following manner: 1-chlorobutanone-2 ⟶ 3-chlorobutanone-2 ⟶ methylacetylcarbinol.

The transformation of $\alpha$-hydroxybutyric aldehyde into methylacetylcarbinol, through the propionylcarbinol, is not very likely on the basis of the polarographic data.

The authors express their indebtedness to S. N. Danilov for his constant interest in the work, and for his many valuable suggestions.

## SUMMARY

1. The half-wave potentials ($E_{1/2}$), the polarographic constants ($i_d/C$), the relation of $\log\frac{i}{i_d-i}$ to E, the apparent consumption of electrons for 1 mole of reducible substance, ($\alpha$), for 1-chlorobutanone-2, 3-chlorobutanone-2, propionylcarbinol and methylacetylcarbinol in the concentration range $1 \cdot 10^{-3}$ to $1 \cdot 10^{-2}$ moles/liter in 0.1 N $NH_4Cl$ and in borate buffer solution at pH = 10,0, have been determined.

2. On the basis of proportionality between wave height and concentration of 1-chlorobutanone-2, 3-chlorobutanone-2, propionylcarbinol and methylacetylcarbinol, the feasibility for their qualitative and quantitative determination, separately, by the polarographic method was determined.

3. On the basis of polarographic data, it can be assumed that propionylcarbinol under the conditions used does not transform into methylacetylcarbinol.

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# INVESTIGATIONS IN THE FIELD OF REDOX TRANSFORMATIONS

## II. POLAROGRAPHIC INVESTIGATION OF BENZOIN, BENZIL, DIACETYL AND ETHYLGLYOXAL

M. I. Bobrova and N. S. Tikhomirova

In the preceding article [1], the authors examined the polarographic characteristics of ketoalcohols belonging to the aliphatic series—propionylcarbinol, $CH_3CH_2COCH_2OH$ and methylacetylcarbinol, $CH_3CHOHCOCH_3$. In the syntheses of these compounds, or in the transformations of these compounds, S. N. Danilov and N. S. Tikhomirova were concerned with their partial oxidation into the corresponding dicarbonyl compounds. It was therefore of interest to know the polarographic characteristics of ethylglyoxal and diacetyl: $CH_3CH_2COCHO$ and $CH_3COCOCH_3$.

For comparison with the aliphatic compounds, at the suggestion of S. N. Danilov, we have studied the redox capacity of aromatic ketoalcohols and diketones: benzoin $C_6H_5COCHOHC_6H_5$ and benzil $C_6H_5COCOC_6H_5$, into which benzoin is easily oxidized, as observed by S. N. Danilov [2].

A series of works has been devoted to the reduction of hydroxycarbonyl compounds at the dropping mercury electrode. Tachi [3] determined the redox potential for benzoin in a medium of 0.01 N HCl +0.1 N KCl by the tangent method. Relative to the normal calomel electrode at a concentration of $10^{-4}$ moles/liter it was found to be equal to −0.953 V. Semerano [4] determined the so-called "molar reduction potential" of benzoin, i.e., the potential at which reduction of benzoin at 1 mole/liter concentration is initiated. According to Semerano's data, it is equal to −1.06 V in 0.1 N $NH_4Cl$ at 50% ethanol. Winkel and Proske [5,6] have determined by extrapolation of the Le Blanc current to zero, the reduction potential value, the so-called "decomposition potential", of benzoin in 0.1 N $NH_4Cl$ solution is equal to −1.22 V. Adkins and Cox [7] determined the reduction potential of benzoin in 0.2 N tetramethylammonium hydroxide solution. Two waves with potentials of −0.7 and −1.4 V were found.

The reduction potential of benzil was found by Tachi to be −0.203 V in 0.01 N HCl + 0.1 N KCl at pH 2, and was found by Winkel and Proske to have the potentials −0.019 and −0.586 V in 0.1 N $NH_4Cl$ solution. The half-wave potentials for benzil in 0.2 N tetramethylammonium hydroxide solution are equal to −0.65 and 1.4 V according to the data of Adkins and Cox. As was indicated by Winkel and Proske, diacetyl in 0.1 N $NH_4Cl$ solution likewise gives two waves of approximately the same height. The reduction potential for the first is equal to −0.7 V, and for the second, −1.58 V; and in 0.1 N LiCl solution, −0.81 and −1.93 V, respectively. Winkel and Proske have found the reduction potential in a medium of 0.01 N HCl + 0.1 N KCl to be equal to −0.4 V; likewise, Tachi found an analogous value for the diacetyl reduction potential in 0.01 N HCl + 0.1 N KCl solution medium, using the tangential method. But this is only an apparent agreement of results, since their methods for determining potentials were different. The reduction of ethylglyoxal was not studied polarographically.

Data obtained by various authors for redox potentials are very inconsistent, as can be seen from this brief review of the works on polarographic reduction of hydroxycarbonyl compounds. They did not determine any of the polarographic constants nor the electron consumption per mole of reducible substance.

## EXPERIMENTAL

Work objectives and method of measurements. The benzoin had a m.p. of 133°, benzil—m.p. 95°, diacetyl—b.p. 87-89°, $n_D^{18}$ 1.3933, as indicated in the literature [8]. The ethylglyoxal was obtained by synthesis from propionylcarbinol with the characteristics: b.p. 110° at 135 mm, $n_D^{20}$ 1.4178, which was in agreement with the literature data [9].

Benzoin and benzil were studied in the concentration range: first, from $1 \cdot 10^{-3}$ to $1.2 \cdot 10^{-2}$ moles/liter, and second, from $2.13 \cdot 10^{-3}$ to $8.6 \cdot 10^{-3}$ moles/liter, diacetyl from $4 \cdot 10^{-3}$ to $6.5 \cdot 10^{-2}$ moles/liter, and ethylglyoxal from $2.2 \cdot 10^{-3}$ to $5.5 \cdot 10^{-3}$ moles/liter.

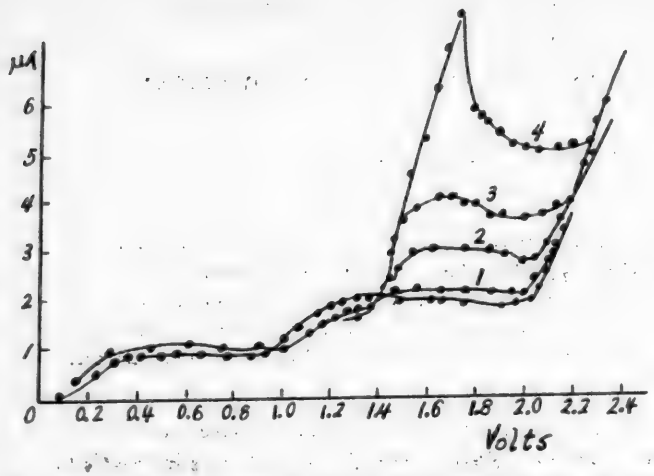


Fig. 1. Benzoin polarograms in 0.02 N $NH_4Cl$ at 78 % $C_2H_5OH$ (20 ml). Weighed portions (g): 1) 0.0043, 2) 0.0156, 3) 0.0276, 4) 0.0476.

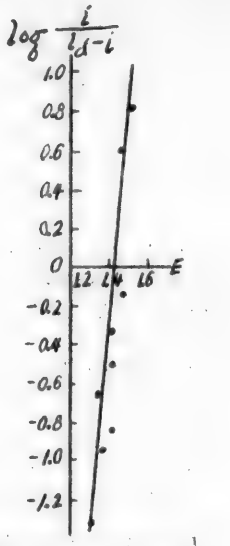


Fig. 2. Relation of $\log \frac{i}{i_d - i}$ to E for benzoin in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$

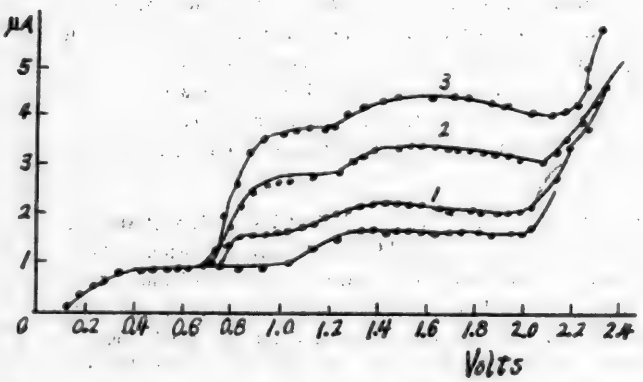


Fig. 3. Polarograms for benzil in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$ (20 ml). Weighed portions (g): 1) 0.0090, 2) 0.0238, 3) 0.0238.

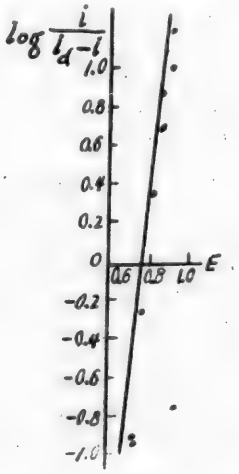


Fig. 4. Function $\log \frac{i}{i_d - i}$ versus E for benzil in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$.

As phonic backgrounds, the electrolytes employed were 0.02 N $NH_4Cl$ in 78% $C_2H_5OH$ and 0.1 N $NH_4Cl$.

Polarography was conducted on a Gorky (factory "standard") polarograph M-7 with a mirror galvanometer, the sensitivity of which is equal to 175 mm/μA on a scale distance of 100 centimeters from the mirror. In the work, shunts from 1/5 to 1/200 of the current sensitivity were used. In all of the experiments an electrolyzer was used, with an internal anode whose potential was regularly determined with reference to the calomel electrode, with the aid of a Rapp's potentiometer. The capillary characteristic: mass of the mercury drop = 0.0025 g, dropping period = 3.75 sec. From this capillary constant $L = m^{\frac{2}{3}} \cdot \tau^{\frac{1}{6}} = 0.956\ mg^{\frac{2}{3}}\ sec.^{-\frac{1}{2}}$. The resistance of the solutions studied was 3000 ohms. All half-wave values ($E_{1/2}$) are referred to the saturated calomel electrode potential with correction for iR.

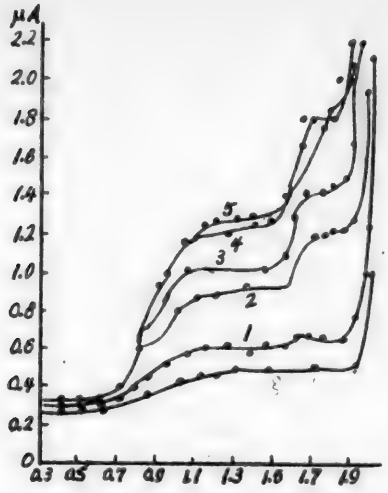


Fig. 5. Polarograms for diacetyl in 0.1 N $NH_4Cl$. Weighed portions (g): 1) 0.0217, 2) 0.715, 3) 0.0877, 4) 0.1127, 5) 0.1127.

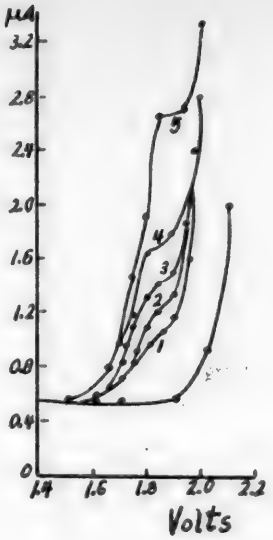


Fig. 6. Polarograms for ethylglyoxal in 0.1 N $NH_4Cl$ (20 ml). Weighed portions (g): 1) 0.0039, 2) 0.0049, 3) 0.0060, 4) 0.0082, 5) 0.0094.

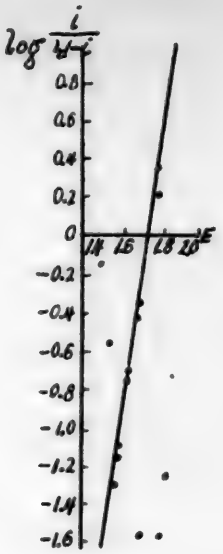


Fig. 7. Relation of $\log \frac{i}{i_d - i}$ to E for ethylglyoxal in 0.1 N $NH_4Cl$.

The polarographic results for benzoin are presented in Fig. 1.* As follows from the data obtained, the reduction of benzoin at the dropping mercury electrode is accompanied by the appearance of one wave with a half-wave potential at $i_d/2 = -1.407$ V, and at $\log\frac{i}{i_d - i} = 0$ $E_{1/2} = -1.434$ V.

The value $E_{1/2}$, increases as the benzoin concentration increases, The benzoin polarographic constant, i.e., the diffusion current, referred to unit concentration, is equal to 735 μ A/g. The function $\log\frac{i}{i_d - i}$ with respect to E is presented in Fig.2. The apparent number of electrons participating in the reduction of 1 mole of substance in the case of an irreversible process [10], is determined from the tangent for the angle of inclination of the straight line, $\log\frac{i}{i_d - i}$ versus E, namely: at 15° $E = E_{1/2} - \frac{0.057}{a} \log\frac{i}{i_d - i}$

$$a = 0.057 \cdot \Delta \frac{\log\frac{i}{i_d - i}}{\Delta E}.$$

The value, $a$, for benzoin upon its reduction in 0.02 N $NH_4Cl$ at 78 % $C_2H_5OH$ is equal to 0.655 (Fig. 2).

The results of benzil polarography in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$ are presented in Fig.3. As can be seen from the polarograms, there appear two waves upon reduction in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$, with half-wave potentials at $i_d/2 = -0.27$ and $-0.750$ V, and at $\log\frac{i}{i_d - i} = 0$, the half wave potential of the second wave is equal to $-0.767$ V. The first wave is very illegible. As the benzil concentration increases, $E_{1/2}$ increases. The polarographic constant for benzil, $i_d/C = 776$ μA/2. The function $\log\frac{i}{i_d - i}$ relative to E is presented in Fig. 4. The value $a$ is equal to 0.992.

Upon reduction of diacetyl in 0.1 N $NH_4Cl$ at the dropping mercury electrode, two waves appear. The half-wave potential ($E_{1/2}$) of the first is at $i_d/2 = 0.784$ V, and of the second, $-1.598$ V. The polarographic constant value ($i_d/C$) for the first wave = 44.7 μA/2, and for the second 30.4 μA/g. The diacetyl polarograms

* On all polarograms the diffusion current values are quoted at 10 times less than the actual.

Polarographic characteristics for benzoin, benzil, diacetyl and ethylglyoxal

| Expt. order no. | Name of substance and phonic electrolyte (20 ml) | Weighed sample (g) | Diffusion current $i_d$ (in μA) | Polarographic constant, $i_d/C$ (in μA/g) | Half-wave potential ($E_{1/2}$) relative to the saturated calomel electrode (in volts) at $i_d/2$ | with correction for iR | at $\log\frac{i}{i_d-i}=0$ | Average value for $E_{1/2}$ (in volts) | Average value for $i_d/C$ (in μA/g) | Electron consumption for one mole of substance, α |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Benzoin in 0.02 N | 0.0043 | – | – | – | – | | | | |
| 2 | $NH_4Cl$ at 78% | 0.0156 | 11.5 | 737 | −1.41 | −1.393 | −1.434 | −1.420 | 735 | 0.655 |
| 3 | $C_2H_5OH$ | 0.0276 | 20.2 | 732 | −1.43 | −1.400 | | | | |
| 4 | | 0.0476 | 35.0 | 735 | −1.48 | −1.427 | | | | |
| 1 | Benzil in 0.02 N $NH_4Cl$ at 78% | 0.0090 | 7.0 | 777 | −0.27<br>−0.76 | −0.749 | | | | |
| 2 | $C_2H_5OH$ | 0.0238 | 18.5 | 777 | −0.27<br>−0.78 | −0.754 | −0.767 | −0.270<br>−0.758 | 776 | 0.992 |
| 3 | | 0.0362 | 28.0 | 774 | −0.27<br>−0.79 | −0.748 | | | | |
| 1 | | 0.0217 | – | – | −0.78<br>−1.58 | – | | | | |
| 2 | | 0.0329 | – | – | −0.75<br>−1.58 | – | | | | |
| 3 | Diacetyl in 0.1 N $NH_4Cl$ | 0.0457 | – | – | −0.79<br>−1.62 | – | | | | |
| 4 | | 0.0715 | 2.6<br>2.8 | 36<br>39 | −0.76<br>−0.62 | – | – | −0.781<br>−1.599 | 34.2<br>33.7 | – |
| 5 | | 0.0877 | 3.6<br>2.8 | 41<br>32 | −0.79<br>−1.59 | – | | | | |
| 6 | | 0.1127 | 5.4<br>4.2 | 47<br>32 | −0.80<br>−1.60 | – | | | | |
| 7 | | 0.1127 | 6.0<br>4.2 | 53<br>32 | −0.80<br>−1.60 | – | | | | |
| 1 | | 0.0039 | 6.7 | 1723 | – | – | | | | |
| 2 | | 0.0049 | 7.6 | 1550 | −1.75 | −1.739 | | | | |
| 3 | | 0.0049 | 7.6 | 1550 | −1.75 | −1.739 | | | | |
| 4 | | 0.0060 | 9.5 | 1587 | −1.72 | −1.706 | | | | |
| 5 | | 0.0060 | 9.5 | 1587 | −1.72 | −1.706 | | | | |
| 6 | Ethylglyoxal in 0.1 N $NH_4Cl$ | 0.0082 | 12.6 | 1536 | −1.72 | −1.700 | | | | |
| 7 | | 0.0082 | 12.8 | 1571 | −1.72 | −1.701 | −1.750 | −1.732 | 1666 | 0.40 |
| 8 | | 0.0082 | 12.8 | 1571 | −1.72 | −1.701 | | | | |
| 9 | | 0.0082 | 12.6 | 1536 | −1.72 | −1.700 | | | | |
| 10 | | 0.0082 | 12.6 | 1536 | −1.72 | −1.700 | | | | |
| 11 | | 0.0094 | 20.9 | 2146 | −1.77 | −1.735 | | | | |
| 12 | | 0.0094 | 19.6 | 2085 | −1.77 | −1.741 | | | | |

are presented in Fig. 5.

The polarographic results for reduction of ethylglyoxal in 0.1 N $NH_4Cl$ are presented in Fig.6. As can be seen from the polarograms, upon reduction of ethylglyoxal in 0.1 N $NH_4Cl$ solution, at the dropping mercury electrode, there appears a wave with the half-wave potential at $i_d/2$, equal to −1.715 V; at $\log\frac{i}{i_d-i}=0$ $E_{1/2}$ equal to −1.75 V. The polarographic constant = 1666 μA/g. The function $\log\frac{i}{i_d-i}$ relative to E is presented in Fig. 7. The value, α, is equal to 0.4.

## EVALUATION OF RESULTS

The polarographic data obtained are presented in the table. A comparison of the benzoin reduction potentials obtained by Semerano [4], by Winkel and Proske [5], and by the authors, has indicated that when the same methods are used for determination, good agreement of results can be obtained, in other words, when using the Semerano method, the benzoin reduction potential = −0.97 V according to our data as compared with Semerano's value of −1.06 V, and when using Winkel and Proske's method, our data give −1.22 V, as compared with Winkel and Proske's −1.22 V. The phonic electrolyte used by Adkins and Cox differ from ours to such a high degree that comparison of our data with that of Adkins and Cox [7] has no meaning.

From a comparison of the benzoin reduction potentials obtained by Tachi [3], Winkel and Proske, and the authors, it follows that the reduction potential for the second wave is equal to −0.60 V, as obtained by the authors, using the same method as that used by Winkel and Proske, which represents good agreement with the results of Winkel and Proske (−0.58 V). The authors, Winkel and Proske, and Tachi are in agreement on the potential value which characterizes the first wave. It should be noted that the first wave is only faintly manifest. The second wave potential of benzil, obtained by the authors and by Winkel and Proske, is close to the reduction potential of Adkins and Cox's first wave. It is true that the phonic electrolyte used by Adkins and Cox is different from that used by the authors and by Winkel and Proske.

It should be noted that upon applying the redox potential method of Winkel and Proske to the data obtained by the authors for diacetyl, the authors have obtained a potential = −0.70 V for the first diacetyl wave, and −1.55 V for the second. The redox potential values obtained agree well with the data of Winkel and Proske (−0.70, −1.58 V).

The benzoin half-wave potential proved to be considerably more positive (−1.420 V) in comparison with the half-wave potential for methylacetylcarbinol (−1.743 V) which indicates a difference due to the effect of the phenyl group as compared with the methyl group upon the reduction of the carbonyl group. The same difference in behavior of phenyl and methyl groups is observed upon comparison of the polarographic data for benzil and for diacetyl − the benzil half-wave potential is considerably more positive (−0.271 and 0.758 V) than the diacetyl half-wave potential (−0.781 and −1.599 V). This again indicates that the proximity of the phenyl group facilitates reduction of the carbonyl group. For the given comparison, certain differences in the phonic electrolyte are disregarded.

Ethylglyoxal reduction proceeds under less favorable conditions (−1.732 V) than that of diacetyl (−0.781, −1.599 V). Consequently the mutual interaction of the adjacent carbonyl groups upon each other favors to a greater extent their reduction at the dropping mercury electrode than does the mutual effect of a ketone and aldehyde grouping.

As seen from the data obtained for the objectives investigated, the presence of a satisfactory proportionality was found between the diffusion current value, i.e., of the wave height versus the concentration of substances. Thus the feasibility of establishing a quantitative analysis for the named objective has been demonstrated.

However, in the case of diacetyl, the small value obtained by the authors for the polarographic constant (34.2 and 33.7 $\mu A/g$) points to some sort of variation, for example diacetyl polymerization. The numerical values for the diffusion current are equal for benzoin and benzil per unit mass of substance being reduced (see table). In the case of ethylglyoxal, the polarographic constant has a high value (1666 $\mu A/g$).

For the binary mixture of benzoin with benzil, there should be three waves on the polarogram: the first two in the more positive region will attest to the presence of benzil (see table), and the third to the presence of benzoin. From the heights of these waves conclusions as to the concentrations of the substances can be drawn. The same can be said regarding binary mixtures of diacetyl with ethylglyoxal and of diacetyl with methylacetylcarbinol [1]. Thus, for the binary mixtures indicated, it is possible to carry out qualitative and quantitative analyses by the polarographic method.

The discharge of electrons per mole of substance being reduced is expressed in all instances, with the exception of benzil, by a fractional value; consequently, the reduction of these substances at the dropping mercury electrode proceeds irreversibly. The apparent electron consumption for benzil exceeds by approximately two times that for diacetyl.

Thus, the three dicarbonyl compounds examined can be arranged in the following order, according to their ability to be reduced at the dropping mercury electrode:

$$\text{benzil} > \text{diacetyl} > \text{ethylglyoxal}$$

which agrees with the structural data for these substances.

## SUMMARY

1. The half potentials ($E_{1/2}$), the polarographic constants ($i_d/C$), the relation of $\log\frac{i}{i_d-i}$ to E, the apparent consumption of electrons upon reduction of one mole of the substance, $a$, were determined for benzoin, benzil, diacetyl and ethylglyoxal in the concentration range $10^{-3}$ to $10^{-2}$ moles / liter in 0.02 N $NH_4Cl$ at 78% $C_2H_5OH$ and in 0.1 N $NH_4Cl$.

2. On the basis of the proportionality between the height of the wave and the concentration for benzoin, benzil, diacetyl and ethylglyoxal, the feasibility for qualitative and quantitative analysis by polarographic means was determined for the separate components and for their mixture.

3. A comparison of the polarographic data for benzoin and methylacetylcarbinol, and for benzil and diacetyl, was carried out. The easier reduction of the carbonyl group when in proximity to the phenyl group was established.

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• See Consultants Bureau translation page 2151.

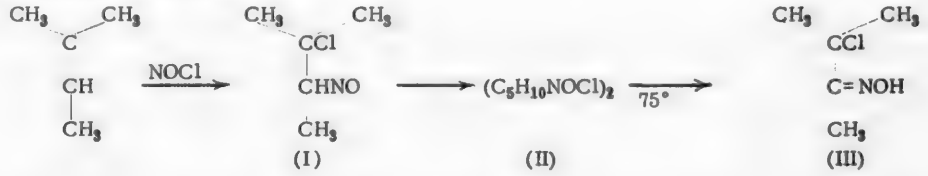
# AN INVESTIGATION OF THE INTERACTION PRODUCTS FROM NITROSYL CHLORIDE AND UNSATURATED HYDROCARBONS

## I. REACTION WITH TRIMETHYLETHYLENE

S. N. Danilov and K. A. Ogloblin

The products of interaction between unsaturated hydrocarbons and nitrosyl chloride might serve as starting materials for the syntheses of various nitrogen compounds, the possibility of which has been insufficiently utilized up to the present time. From our point of view the most interesting seems to be the utilization of nitrosochlorides for the synthesis of various oximes and amines of compounds which are relatively inaccessible and insufficiently investigated. This determined the content of the present work. As the first objective in the investigation, the nitrosochloride of trimethylethylene has been selected.

The structure and certain transformations of trimethylethylene nitrosochloride were established by the works of Wallach [1] and Schmidt. The latter [2] considers that when nitrosyl chloride is reacted with trimethylethylene*, there is formed at first a monomeric blue liquid nitrosochloride (I), which then transforms into a crystalline product (II), with m.p. 74-75°. The properties and reactions of the latter indicate that this true nitroso compound is the dimer of the initial product of reaction. Dimer (II), upon prolonged heating at its melting point (75°) converts into chloroxime (III), crystals with m.p. 49-50° (from ligroin). The transformations indicated occur according to the scheme




Upon reaction of (III) with sodium methylate, the corresponding methoxy derivative was obtained, and upon boiling with concentrated hydrochloric acid there was obtained the keto alcohol, 2-methylbutanol-2-one-3 [2]**. Schmidt observed only the formation of ammonia [3] upon reduction of (II) and (III) by different methods for the purpose of obtaining the amine.

To achieve our purpose – conversion to oximes and amines – the reactive chloroxime (III) could serve as the starting substance. As has already been indicated, the yield of (II) in the Schmidt experiments consisted of only 15-26%, which did not satisfy us as well as the method for transformation of (II) into (III). The authors have obtained (II) by reaction of nitrosyl chloride with trimethylethylene in ether solution, with a yield of 50%. At the same time were always formed liquid products, blue in color.

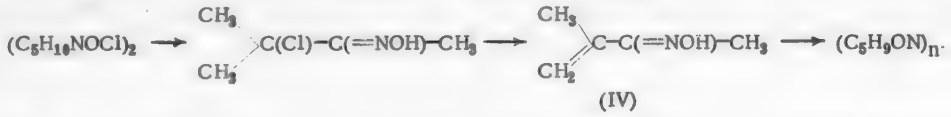
The authors have observed that nitrosochloride (II), although stable when allowed to stand in the open air for considerable time, will decompose rapidly when stored in a closed container; the crystals become moist, hydrogen chloride is evolved, the characteristic signs of the chloroxime (III) appear – sharp, piercing odor, and lachrymatory action. The decomposition process terminates with the formation of a hard, yellow, odorless polymer.

The assumption made that the decomposition of (II) is induced by the action of hydrogen chloride, at least in the first stage of chloroxime (III) formation, has been confirmed experimentally. The nitrosochloride (II), after the lapse of a certain time in hydrogen chloride-saturated ether solution, is transformed into the chloroxime (III) in yield of 75-80%. The same process occurs if the reaction products of trimethylethylene with nitrosyl chloride - dimer (II), and the blue liquid are subjected to hydrogen chloride action. The crystals

* The nitrosochloride of trimethylethylene was obtained by Schmidt upon reaction of hydrochloric acid with a mixture of trimethylethylene and amyl nitrite, with a yield of 15-26%.

** The author does not indicate the yields of products

of dimer gradually disappear, and from the blue solution, upon cooling, can be separated the chloroxime (III) in considerable yield The processes taking place when the nitrosochloride (II) decomposes upon storage in a closed container, can apparently be represented by the following scheme:

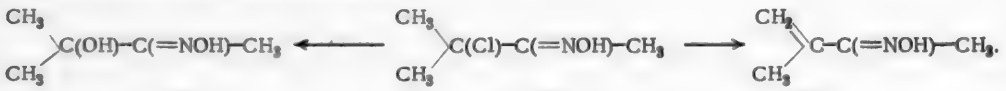


(IV)

The first part of the scheme is experimentally confirmed. The chloroxime apparently then splits off hydrogen chloride and converts into the oxime of methylisopropenylketone (IV) which polymerizes under the conditions indicated to form a hard yellow polymer, similar to the polymer from methylisopropenylketone [4].

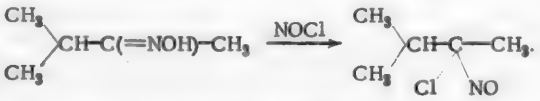
The method for transformation of (II) into (III), derived by the authors, is better than the method proposed by Schmidt, which requires maintenance of strict temperature control (75°), disturbance of which, according to Schmidt himself, and other authors [5], results in complete decomposition of the product; therefore, the Schmidt method is unsuited for obtaining considerable quantities of (II).

It was not possible to separate the individual compounds from the blue liquid products after separation of the crystals of (II), by distillation in vacuo, because at the same time decomposition starts with the formation of dark resin, and the evolution of a large volume of gas. Upon treatment of the blue liquid with calcium carbonate and sodium bicarbonate, in the presence of water, small quantities of dimethylacetylcarbinol oxime (V) and methylisopropylenylketone oxime (IV) were obtained. The two compounds could be formed only in the presence of the reaction products of chloroxime (III):

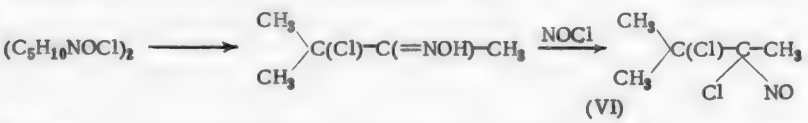


(V) (III) (IV)

Upon synthesis of (II) under conditions of large nitrosyl chloride excess, it is possible to separate a crystalline substance, blue in color, from the reaction mixture, which corresponds, according to analysis, to the dichlornitroso compound $C_5H_9ONCl_2$ (VI). From the literature data [6] it is known that there are formed for example from the action of nitrosyl chloride on ketoximes, chloronitroso compounds with the chlorine and the nitroso group attached at the same carbon atom:



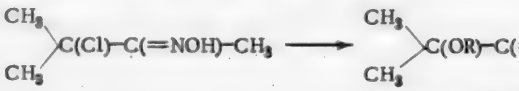
In our case the formation of the blue crystals can be illustrated by the scheme:



(VI)

In addition, from the blue liquid is separated the dichloride $C_5H_{10}Cl_2$.

The chlorine atom in the chloroxime (III) is characterized by great mobility. The authors have found that upon shaking with water for a few minutes the substance transforms completely into the dimethylacetylcarbinol oxime (V). Upon heating a solution of the chloroxime in methyl and ethyl alcohols, in the presence of calcium carbonate or sodium bicarbonate, the corresponding methyl and ethyl esters of dimethylacetylcarbinol are readily formed (VII) and (VIII). Upon reaction with potassium acetate, the corresponding acetic ester (IX) was obtained:



where R = $CH_3$–(VII), $C_2H_5$–(VIII), $CH_3CO$–(IX).

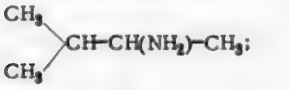
The unsaturated oxime (IV) is easily obtained from the chloroxime (III) on reaction in ether solution with sodium bicarbonate.

It is of interest to note that compound (IV) is derived first in the form of a hard solid, then in a liquid modification form, at which time the liquid modification gradually converts into the solid.

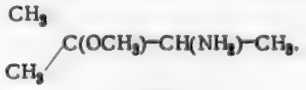
The oxime (IV) is formed likewise from (III), upon reaction with sodium ethylate, but in smaller yield, due to the formation of dimer and trimer.*

The compounds (IV), (V) and (VII) were subjected to catalytic hydrogenation with Raney nickel for the purpose of obtaining the amines and (III) was chemically reduced by means of stannous chloride. In the latter instance only a negligible quantity of 2-methyl-3-aminobutane hydrochloride could be obtained. Catalytic hydrogenation was carried out at room temperature and normal pressure. The saturated amine, 2-methyl-3-aminobutane, was obtained from (IV) with a yield up to 40%, at which time a considerable portion of oxime was split, forming ammonia. For substantiation of the amine structure obtained from (IV), hydrogenation of the saturated methylisopropylketoxime was carried out. The amine (X) obtained in 83% yield was found to be identical with the amine from (IV).

Upon hydrogenation of (VII), 2-methyl-2-methoxy-3-aminobutane (XI) was obtained:

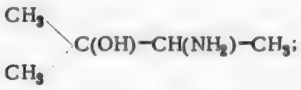


(X)

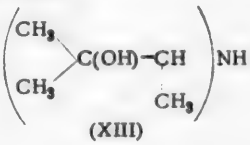


(XI)

Upon hydrogenation of (V), there was obtained with yields up to 70%, the aminoalcohol (XII). Along with it resulted a small quantity of secondary oxamine (XIII):



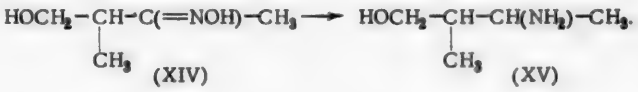
(XII)



(XIII)

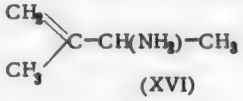
Hydrogenation of (V) was carried out in absolute ethanol, in crude alcohol, in crude alcohol containing 10% ammonia, and in methanol, at which time the yields of (XII) in these latter three instances were respectively 51, 47 and 44% of the theoretical.

For comparison, catalytic hydrogenation of the oxime with the same carbon chain was carried out, but with the primary alcohol group, namely, the oxime of 2-methylbutanol-1-one-3 (XIV). The corresponding amino alcohol, 2-methyl-3-aminobutanol-1 (XV) was obtained at 52% of theoretical.



(XIV) (XV)

The amino alcohols (XII) and (XV) underwent dehydrattion by means of sulfuric acid, for the purpose of obtaining the unsaturated amine. In both cases the unsaturated amine, 2-methyl-3-aminobutene-1 (XVI) was obtained, at which time its yield from (XII) was considerably greater than from (XV).



(XVI)

The boiling point, density and index of refraction of the amine (XVI) were found to be noticeably higher than the same for amine (X).

## EXPERIMENTAL**

Trimethylethylene Synthesis. 200 g of isoamyl alcohol, with b.p. 128-132°, was passed through a porcelain tube containing aluminum sulfate catalyst at 400-415° for 3.5 hours. 101 g of hydrocarbon fraction was obtained with b.p. 20-40° (63.5% of the theoretical yield based on alcohol passed through). Upon fractional distillation over sodium,

* Oxime (IV) and its dimer and trimer were obtained by Wallach upon reaction of sodium ethylate with trimethylethylene nitrosate [7].

** A. N. Shirshova assisted in the experimental part.

the fractions obtained were 18.5-23°-15 g (14.8%) 23-37.7°-40.2 g (39.8%); 37.7-38.6°-41 g (40.6%).

Nitrosylsulfuric Acid and Nitrosyl Chloride Synthesis. The nitric oxides obtained from the reaction of nitric acid (specific gravity 1.4) with copper shavings were passed, after drying with calcium chloride, through two absorption flasks containing sulfuric acid (specific gravity 1.84). The precipitated crystals of nitrosylsulfuric acid were separated from the mother liquor.

Nitrosyl chloride was obtained by gentle heating of a mixture of finely ground and sifted anhydrous sodium chloride (taken in slight excess) with nitrosylsulfuric acid. The gas, after passing through a calcium chloride tube, was condensed in a flask cooled to minus 45-50°. The yield of nitrosyl chloride was 71-74% of theoretical, based upon nitrosylsulfuric acid.

Trimethylethylene Nitrosochloride (II) Synthesis. Nitrosyl chloride, obtained from 160 g (1.25 moles) of nitrosylsulfuric acid and 90 g of sodium chloride (1.5 moles), was passed into a solution of 51.5 g of trimethylethylene (b.p. 37.5-38.2, $n_{\alpha}^{20}$ 1.3852) in 100 ml of absolute ether, with stirring and salt-ice cooling for 2 hours and 25 min. 48.5 g of crystals, b.p. 70-71.5 (yield 48 7% of theoretical) was separated from the reaction mixture. From their properties the crystals corresponded to trimethylethylene nitrosylchloride [2].

2-Methyl-2-chlorbutanone-3 Oxime (III) Synthesis. a) Nitrosyl chloride (from 100 g of nitrosylsulfuric acid and 60 g of sodium chloride) was passed into a solution of 37 g of trimethylethylene (b.p. 38-39.5, $n_{\alpha}^{16}$ 1.3875) in 50 ml of absolute ether cooled by salt-ice mixture, and stirred, for 3 hours, and for 20-25 minutes hydrogen chloride was passed through. The reaction mixture—blue liquid and colorless crystals (II)—was left at room temperature. After 48 hours the crystals were sucked off from the mother liquor, and on cooling the blue liquid another portion of crystals separated. After 48 hours standing in a sulfuric acid vacuum dessicator the weight of portion I was 14.65 g, m.p. 43-50°; portion II weight was 19.38 g, m.p. 42-49°. After recrystallization from benzene (b.p. 40-60°) three portions of 2-methyl-2-chlorbutanone-3- oxime with m.p. 48-49°, 47-48° and 45-46° respectively were obtained. The substance with m.p. 45-46° was analyzed.

0.1070 g substance: 9.7 ml $N_2$ (17°, 761 mm). 0.1013 g substance: 9.2 ml $N_2$ (17°, 764 mm). Found %: N 10.60, 10.66. $C_5H_{10}ONCl$. Calculated %: N: 10.33. 0.0958 g substance; 16.61 g benzene: $\Delta t$ 0.155°. 0.2498 g substance; 16.61 g benzene: $\Delta t$ 0.390°. Found: M 192.7, 200.7. $C_5H_{10}ONCl$. Calculated: M 135.5. $(C_5H_{10}ONCl)_2$. Calculated: M 271.0;

Literature data for 2-methyl-2-chlorbutanone-3: m.p. 49-50° [2].

b) Dry hydrogen chloride was passed through a saturated solution of 12.8 g of II (m.p. 70-71.5°) in absolute ether for 1 hour, and the reaction mixture then left for 24 hours at room temperature. On the following day the ether was sucked off in a vacuum dessicator, 9.8 g of hard solid product was obtained with the odor of chloroxime (III). It was recrystallized from benzene (40-60°). M.p. 47-48°. A small portion, remaining undissolved in the benzene, was found to be hydroxylamine hydrochloride.

Interaction of Trimethylethylene with Nitrosyl Chloride, the Latter in Excess. Nitrosyl chloride (from 130 g of nitrosylsulfuric acid and 70 g of sodium chloride) was passed through a solution of trimethylethylene (32.5 g, b.p. 37.2-38.5°, $n_{\alpha}^{19.6}$ 1.3852) in absolute ether (50 ml) for four hours, with stirring and salt-ice cooling. The considerable quantity of flaky crystals on the bottom of the flask was identified as the nitrosochloride (II). The method liquor was brown in color with a greenish tint (excess of NOCl). The reaction mixture was left for 72 hours at room temperature. After 24 hours there were no crystals on the bottom, and the color of the liquid was dark blue. After 48 more hours the crystals which formed on the bottom were separated and dried. The weight, 7 g., m.p. 144-145°. It was identified as hydroxylamine hydrochloride.

There was separated upon distillation of the blue liquid in vacuo: 1) a slightly blue liquid, with b.p. 22-35° at 24 mm, weight 13 g; 2) blue crystals, subliming when distilled in the temperature range 32-40° at 7 mm, weight 2 g. Upon distillation in vacuo of the residue boiling above 69° at 7 mm (dirty-yellow liquid) violent decomposition occurred with the evolution of a large amount of gas (nitric oxide) and effervescence. Everything was converted into a brownish-black resin.

Upon distillation there was separated from the sky-blue liquid a fraction with b.p. 114-117° (772 mm);

$d_4^{20}$ 1.0082; $n_D^{20}$ 1.4210; $MR_D$ 35.46. $C_5H_{10}Cl_2$; Calculated 35.02.

Blue Crystals. In color they resembled copper sulfate crystals. The odor was sharp, strongly lachrymatory, highly volatile in air and in vacuo, insoluble in water. Upon prolonged heating with water they disintegrated, the blue color disappearing; the solution was acid in reaction. Easily soluble in ether, in petroleum

ether, benzene, carbon tetrachloride, methanol, ethyl acetate, less readily in ethanol. M.p. of the non-crystallized substance 103.5°; blue at melting temperature, yellow-green at 110°.

0.0801 g substance: 5.7 ml $N_2$ (21°, 779 mm). 0.1124 g substance: 0.1856 g AgCl (Carius) 0.0928 g substance; 16.75 g benzene: Δt 0.160°. 0.1043 g substance; 13.75 g benzene: Δt 0.23°. Found %: N 8.37; Cl 40.84; M 177.4, 169.1. $C_5H_9ONCl_2$. Calculated %: N 8.23; Cl 41.74; M 170.0.

Thus, the structure 2-methyl-2,3-dichlor-3-nitrosobutane (VI) should be ascribed to the substance.

2-Methylbutanol-2-one-3 oxime (V) Synthesis. 2 g of the chloroxime (III) of m.p. 46-47° was shaken with 20 ml of water at room temperature. All was dissolved after 15 minutes, the solution was neutralized with sodium hydroxide and saturated with sodium chloride. The white flakes which floated up were extracted with ether, and after evaporation of the ether there was obtained 1.05 g of crystals with m.p. 86.5-88.5° and 0.62 g of crystals with m.p. 85-90°. The yield of crude product was 94.2% of the theoretical. After recrystallization from absolute ether the m.p. was 86-87°. A sample mixed with dimethylacetylcarbinol oxime, specially obtained by [8], melted at 86-87°.

2-Methyl-2-methoxybutanone-3 oxime (VII) Synthesis. A mixture of 11.4 g of the chloroxime (III), 80 ml of methyl alcohol and 20 g of calcium carbonate was heated to the boiling point of alcohol for 1 hour, with stirring, and then left for the night. On the following day, after separation of the calcium carbonate, the greater part of the alcohol was distilled off in vacuo under gentle heating, the precipitated crystals sucked off, dried, and weighed. The weight was 9.6 g. Yield of crude product was 87.1% of the theoretical.

After recrystallization from benzene (b.p. 40-60°) there was obtained 6.7 g of substance with m.p. 89-90° and 0.2 g with m.p. 85-86°. The yield for the first portion was 60.8% of the theoretical.

0.1054 g substance: 10.2 ml $N_2$ (21°, 752 mm). 0.0963 g substance: 9.3 ml $N_2$ (22°, 759.5 mm). 0.0820 g substance: 16.1 ml $CH_4$ (13°, 759 mm). Found %: N 11.01, 11.05. Active H atoms 1.08. $C_6H_{13}O_2N$. Calculated %: N 10.68. Active H atoms 1.00. According to literature data [2], m.p. 92°.

2-Methyl-2-ethoxybutanone-3-Oxime (VIII) Synthesis. A mixture of 3 g of the chloroxime (III) with m.p. 47-48°, 7 g of calcium carbonate and 20 ml of redistilled ethanol was heated with stirring for 2 hours and 40 mintues, at a temperature of 70-80°, and then left for the night. On the following day the mineral salts were separated from the transparent liquid, the alcohol distilled off, and the residue twice distilled in vacuo. 1.5 g of colorless liquid of weak odor, with b.p. 84-85° at 8 mm was obtained:

$n_\alpha^{20}$ 1.4465.

0.1110 g substance: 9.9 ml $N_2$ (18°, 771 mm). (Dumas). 0.1144 g substance: 10.25 ml $N_2$ (23°, 772 mm). Found %: N 10.52, 10.38. $C_7H_{15}O_2N$. Calculated %: 9.65.

Ketoximes with several methyl grups give too high a value for nitrogen by the Dumas method [9].

2-Methyl-2-acetoxybutanone-3 Oxime (IX) Synthesis. A mixture of an ether solution of the chloroxime (III) with anhydrous potassium acetate was stirred at the temperature of boiling ether for 4 hours and 30 min. After separation of the salts from the ether solution, 2/3 of the ether was distilled off, and the residue poured into a beaker. The precipitated crystals were pressed out on a filter paper, m.p. 92-99°. After recrystallization from ligroin – snow-white needles, m.p. 102-103°. The sample mixed with a known sample obtained by another method [8], melted at 101-102°.

2-Methylbutene-1-one-3 Oxime (IV) Synthesis. a) A solution of 16 g of the chloroxime (III), of m.p. 47-49°, in 80 ml of absolute ether, was stirred for 6 hours and 20 minutes at the boiling temperature of ether on reflux with 20 g of sodium bicarbonate. On the following day a yellowish transparent solution was separated from the mineral salts, ther ether distilled off at normal pressure, and the residue distilled in vacuo. 6.5 g of the oxime (IV), with b.p. 65-67° at 11 mm, was obtained, which crystallized in the receivor. M.p. 43-44°. Yield 55.5% of the theoretical

0.1237 g substance: 16.1 ml $N_2$ (19°, 730 mm). 0.1644 g substance: 21.5 ml $N_2$ (20.5°, 727.5 mm). 0.0726 g substance; 15.79 g benzene: Δt 0.16°. 0.0648 g substance; 18.80 g benzene: Δt 0.132°. Found %: N 14.29, 14.13; M 148, 135. $C_5H_9ON$. Calculated %: N 14.14; M 99.

The crystals dissolved readily in benzene, ether, alcohol, ethyl acetate, and poorly in water. After

6 months the crystals over calcium chloride in a dessicator yellowed slightly, but the melting point remained unchanged. From the literature data: [7]: m.p. 44-45°.

b) In a second experiment, using a mixture of sodium bicarbonate and calcium carbonate, there was separated from the reaction products a colorless liquid with the odor of oxime (IV), and b.p. 68° at 8 mm. After 24 hours it was 1/3 crystallized. The m.p. of the crystals was 43-44°, a sample of which when mixed with the oxime of the preceding experiment melted at 43-44°. The liquid separated from the crystals did not crystallize when seeded with an oxime crystal and cooled.

$d_4^{19}$ 0.9529; $n_D^{19}$ 1.4833; $MR_D$ 29.71; calculated 29.02.

0.1376 g substance: 17.4 ml $N_2$ (21°, 757 mm). 0.1355 g substance: 17.4 ml $N_2$ (18°, 746.5 mm). Found %: N 14.26, 14.45. $C_5H_9ON$. Calculated %: N 14.14.

After 24 hours further crystallization of the liquid began in the pycnometer, and after standing 10 days crystallized completely.

Reduction of the Chloroxime (III) with Stannous Chloride. 2.4 g of the chloroxime in 25 ml of absolute ether was added, with snow-salt cooling, to a solution of 15 g of stannous chloride in 50 ml of absolute ether, saturated with hydrogen chloride. On the following day there appeared on the bottom of the flask colorless needle crystals. They were dissolved in water, and through the solution was passed hydrogen sulfide and the precipitated stannous sulfide separated; a small amount of colorless crystals with m.p. 210° was obtained by evaporation of the filtrate in a vacuum dessicator over sulfuric acid. Upon reaction with alkaline solution — an amine odor. M.p. of the HCl salt of the 2-methyl-3-aminobutane was 210°.

Catalytic Hydrogenation of 2-Methylbutene-1-one-3 Oxime (IV)*. a) 6.72 g of the oxime in 100 ml of absolute alcohol was hydrogenated in the presence of Raney nickel. Hydrogenation ceased after absorption of 3170 ml of hydrogen (0°, 760 mm), required for addition, by calculation $2H_2$ 3041 ml, $3H_2$ 4561 ml. After appropriate treatment a fraction was obtained with b.p. 85-85.5° at 764 mm, 0.7 g, $n_D^{20}$ 1.4060. It was a colorless, highly mobile volatile liquid with strong amine odor. Bromine water was instantly decolorized, a solution of potassium permanganate was decolorized within 15-20 minutes.

0.0791 g substance: 11.5 ml $N_2$ (23°, 764 mm). 0.0873 g substance: 12.6 ml $N_2$ (23.5°, 760 mm). Found %: N 16.69, 16.41. $C_5H_{13}N$. Calculated %: N 16.07.

The hydrochloride salt was obtained by passing hydrogen chloride into an ether solution of the amine. M.p. 210° (from acetone).

0.0638 g substance: 0.0747 g AgCl. 0.0561 g substance: 0.0656 g AgCl. Found %: Cl 28.97. 28.93. $C_5H_{13}N \cdot HCl$. Calculated %: Cl 28.69.

b) The oxime (IV) was a liquid, b.p. 67.5-71° at 12 mm, $n_D^{18.5}$ 1.483. Weight 3.45 g, 30 ml of absolute alcohol, 2 g of nickel catalyst. 2230 ml of hydrogen (0°, 760 mm) was absorbed, required for addition, according to calculation $3H_2$ 2342 ml. After appropriate treatment the amine fractions were separated (at 761 mm); 1) b.p. 82-84° - 0.2 g, $n_D^{23}$ 1.4047; 2) b.p. 85-86.5° - 1.12 g. The yield for the two fractions was 44% of the theoretical.

For the fraction with b.p. 85-86.5°:

$d_4^{23}$ 0.7478; $n_D^{23}$ 1.4047; $MR_D$ 28.53; calculated 28.71.

0.1015 g substance: 14.6 ml $N_2$ (21°, 761.5 mm). Found %: N 16.48. $C_5H_{13}N$. Calculated %: N 16.07.

Literature data for 2-methyl-3-aminobutane [10]: b.p. 83-84°, $d^{18.5}$ 1.7574.

2-Methyl-3-aminobutane (X) Synthesis. 7.63 g of 2-methylbutanone-3 oxime (b.p. 155-160°) in 50 ml of absolute alcohol was hydrogenated to the completion of hydrogen absorption. 3056 ml of hydrogen was absorbed, required amount being 3386 ml. After appropriate treatment 7.57 g of the hydrogen chloride salt of 2-methyl-3-aminobutane, or 83.3% yield of theoretical, was obtained. M.p. 208-209° (from acetone). A sample mixed with the amine salt obtained from (IV) melted at 208-209°.

2-Methyl-2-methoxy-3-aminobutane (XI) Synthesis. 2 g of the oxime (VII) with m.p. 89-90° in 90 ml of absolute alcohol. 476 ml of hydrogen was absorbed, 684 ml being required. After appropriate treatment, 0.3 g of amine with b.p. 133-133.5 at 757 mm was obtained. Colorless liquid with amine odor.

0.0914 g substance: 9.6 ml $N_2$ (20°, 769 mm). Found %: N 12.26. $C_6H_{15}ON$. Calculated %: N 11.96.

* Hydrogenation in all of the instances described below was carried out under normal conditions in the presence of Raney nickel. The hydrogen volume was corrected to 0° and 760 mm.

2-Methyl-3-aminobutanol-2 (XII) Synthesis. 15 g of the oxime (V) with m.p. 86-88° in absolute ethyl ether solution was hydrogenated to the cessation of hydrogen absorption. 5668 ml of hydrogen was absorbed, 5743 ml ($2H_2$) is required. After separation of catalyst, distillation of the alcohol, and two distillations, the following fractions were obtained (at 764 mm): 1) up to 152° - 0.8 g; 2) 152-156° - 1.0 g; 3) 156-159° - 6.0 g; 4) above 159° - 1.0 g. The yield for the 156-159° fraction was 45.4% of the theoretical.

$d_4^{19.5}$ 0.9256; $n_D^{19.5}$ 1.4497; $MR_D$ 29.92; calculated 30.24.

0.0713 g substance: 8.3 ml $N_2$ (23°, 765 mm). Found %: N 13.38. $C_5H_{13}ON$. Calculated %: N 13.58.

Literature data [11]: b.p. 157-158° (743 mm), $d_{15}^{15}$ 0.9291.

Below is given a summary of 2-methyl-3-aminobutanol-2 yield upon hydrogenation of the oxime (V) in various experiments.

| Order No. | Solvent | Oxime taken (g) | Fractions obtained 154-180° (g) | 180-212° (g) | Yield for 154-180° frac. (%) | Note |
|---|---|---|---|---|---|---|
| 1 | Absolute ethanol | 20 | 12.25 | 2.72 | 70 | Spontaneously crystallized |
| 2 | The same | 18.1 | 12.03 | 1.87 | 75.4 | |
| 3 | Crude ethanol | 5.24 | 2.74 | 1.0 | 50.9 | |
| 4 | 10% $NH_3$ solution in crude alcohol | 10 | 4.1 | 2.3 | 46.6 | |
| 5 | Methanol | 5 | 1.95 | 1.0 | 44.3 | |

From the above-boiling fractions obtained in the experimental series, a substance with b.p. 75-76.5° at 7 mm was separated, corresponding to the secondary oxamine (XIII). Literature data for (XIII): b.p. 252-254 at 757 mm [12]. M.p. about 30°.

0.1281 g substance: 8.3 ml $N_2$ (20°, 778 mm). Found %: N 7.67. $(C_5H_{11}O)_2NH$. Calculated %: N 7.40.

2-Methyl-3-aminobutanol-1 (XV) Synthesis. 2-Methylbutanol-1-one-3 was obtained by condensation of methylethylketone with formaldehyde.* The oxime (XIV) was obtained from it by the usual procedure, in 77% yield of theoretical – a viscous liquid with b.p. 134-135° at 15 mm, which rapidly crystallized, m p. 42-44°

0.1029 g substance: 10.8 ml $N_2$ (23°, 764 mm). Found %: N 12.03. $C_5H_{11}O_2N$. Calculated %: N 11.96.

Literature data for (XIV) [15]: b.p. 144° at 20 mm.

20 g of crystalline oxime (XIV) was hydrogenated in 105 ml of absolute alcohol solution to the cessation of hydrogen absorption. 7609 ml of hydrogen was absorbed, 7658 ml being required. The catalyst was separated and the alcohol distilled off. Upon distillation the following fractions were obtained (at 770 mm): 1) b.p. 191-192° - 3.2 g, $n_D^{20}$ 1.4570; 2)b.p. 192-194°–6.0 g, $n_D^{20}$ 1.4576. Yield for the two fractions was 52.3%. Upon subsequent distillation the fraction with b.p. 194° at 770 mm was separated. Viscous, colorless liquid with an ammoniacal odor.

$d_4^{20}$ 0.9389; $n_D^{20}$ 1.4576; $MR_D$ 29.94; calculated 30.24.

0.0868 g substance: 10.2 ml $N_2$ (22°, 771 mm). Found %: N 13.66. $C_5H_{13}ON$. Calculated %: N 13.58.

2-Methyl-3-aminobutene-1 (XVI) Synthesis. a) 2-Methyl-3-aminobutanol-2 (XII) Dehydration. A solution of 6 g of sulfuric acid (specific gravity 1.84) in 10 ml of water was poured into 6.1 g of the amino alcohol in 10 ml of water solution cooled with ice. The mixture was distilled at 30 mm on a Wood's alloy bath for 4 hours and 10 minutes. The Wood's alloy temperature at the start was 90°, and at the end 143°. In the flask – a viscous dark liquid with greenish tint. Left for the night. The following day a solution of 20 g of sodium hydroxide in 30 ml of water was poured into the flask, and the amine was distilled off. The distillate stood over KOH granules for 2 hours, the upper layer was then separated and distilled over KOH. The fractions obtained (at 770 mm) were: 1) 85-88° - 0.67 g, $n_D^{20}$ 1.4267; 2) 88-89° 1.7 g. The yield for the two fractions was 47% of theory.

Fraction 2 – a colorless, volatile, highly mobile liquid with a very sharp ammoniacal odor.

$d_4^{20}$ 0.7785; $n_D^{20}$ 1.4274; $MR_D$ 28.09; calculated 28.24.

* See [13], and also [14].

0.0911 g substance: 12.8 ml $N_2$ (21°, 772.6 mm). 0.1312 g substance: 18.7 ml $N_2$ (21°, 768.3 mm). Found %: N 16.44, 16.59. $C_6H_{11}N$. Calculated %: N 16.45.

Hydrogen Chloride Salt was obtained by passing dry hydrogen chloride into an ether solution of the amine. The salt was highly hygroscopic. It was purified by precipitation from alcohol solution by absolute ether. M.p. 153-153.5°. After a second precipitation m.p. was 153-153.5°.

Picrate - long, thin, scaly needles, yellow in color. M.p. 171-172° (from dilute alcohol). The amine (XVI) was obtained in 54.3% yield in the second experiment. For the fraction with b.p. 87.5-89.5 at 750 mm was found:

$d_4^{20}$ 0.7784; $n_D^{20}$ 1.4265; $MR_D$ 28.06; calculated 28.24; $d_4^{23.4}$ 0.7752; $n_\alpha^{23.4}$ 1.4210; $MR_\alpha$ 27.85; calculated 28.07.

b) Dehydration of 2-Methyl-3-aminobutanol-1 (XV). Under the same conditions as was described in the preceding experiment, there was obtained upon dehydration of 6.5 g of (XV), a fraction with b.p. 89-94° in the amount of 0.8 g. Due to the small amount of substance, it could not be purified further.

$d_4^{20}$ 0.8132; $n_D^{10.5}$ 1.4305; $n_D^{20}$ 1.4260.

## SUMMARY


1. The conditions were determined for carrying out the reaction between trimethylethylene and nitrosyl chloride in order to obtain either the nitrosochloride (II) or the chloroxime (III). It was demonstrated that transformation of (II) into (III) occurs easily under the action of hydrogen chloride in ether solution. 2-Methyl-2,3-dichlor-3-nitrosobutane (VI), not described in the literature, was separated from the reaction products during the synthesis of II, using excess nitrosyl chloride.

2. A procedure was found for obtaining hydroxy-, methoxy-, ethoxy- and acetoxy-substituted derivatives of 2-methylbutanone-3-oxime from the chloroxime (III), and similarly of methylisopropenylketone oxime.

3. The catalytic hydrogenation on Raney nickel of: methylisopropenylketone, methylisopropylketone, methylhydroxyisopropylketone, methylmethoxyisopropylketone and β-methyl-γ-keto-butanol oxime was carried out. The corresponding amines were obtained, among them 2-methyl-2-methoxy-3-aminobutane and 2-methyl-3-amintobutanol-1 not mentioned in the literature.

4. Upon dehydration of 2-methyl-3-aminobutanol-2 and 2-methyl-3-amino-butanol-1 there was obtained the unsaturated 2-methyl-3-aminobutene-1 amine, not mentioned in the literature.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# AN INVESTIGATION OF THE INTERACTION PRODUCTS FROM NITROSYL CHLORIDE AND UNSATURATED HYDROCARBONS

## II. REACTION WITH ISOBUTYLENE

K. A. Ogloblin

As is known, isobutylene gives with nitrosyl chloride a crystalline product (I), to which is ascribed the structure of the dimerized oxime of α-chlorisobutyric aldehyde, although there is no proof of such a structure in the literature. Upon heating of (I) with hydrochloric acid, it was not possible to separate any individual compound, and, among the reaction products it was only possible to prove qualitatively the presence of the aldehyde group [1,2].

To the author it was of interest also to examine compound (I) while continuing an investigation of the interaction products of nitrosyl chloride with unsaturated hydrocarbons.

In the preceding article [3] the authors demonstrated that the chlorine atom in 2-chloro-2-methylbutanone-3 oxime has great mobility and transforms easily to a hydroxyl or alkoxyl group, which is apparently explained by its position at the tertiary carbon atom, and by the presence in the α,β-position of the double bond between carbon and nitrogen. It can be assumed that chlorine, likewise, will possess similar properties in α-chlorisobutyric aldoxime.

If, however, product (I) appears to be the oxime of α-chlorisobutyric aldehyde dimer, then under the appropriate conditions there might be obtained from it the α-substituted oxime of isobutyric aldehyde. In addition to being useful for the synthesis of various nitrogen compounds from isobutylene, the transformations indicated could serve as sufficiently convincing proof of both the structure for (I) and of α-chlorisobutyric aldoxime in the dimer form.

The oxime of 2-chloro-2-methylbutanone-3, obtained from the chloronitro compound of trimethylene by simply shaking with water for a few minutes, transforms completely into the oxime of 2-methylbutanol-2-one-3 ketoalcohol [3]. Considering the fact that (I) seems to be the dimer of α-chlorisobutyric aldoxime, it could be expected that the substitution reaction of chlorine for hydroxyl will not proceed easily. In fact, the indicated transformation proceeds only upon heating, at which time the first stage of the reaction is apparently the transformation of dimer (I) into the monomer (II), which then enters into reaction with water to form α-hydroxyisobutyric aldoxime:

$$(C_4H_8NOCl)_2 \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C(Cl)\!-\!CH\!=\!NOH \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C(OH)\!-\!CH\!=\!NOH.$$

(I) (II) (III)

The reaction was carried out in the presence of finely-ground calcium carbonate, and completion of reaction was determined by cessation of carbon dioxide evolution.

By substituting various alcohols for water, there can be obtained the corresponding α-alkoxyderivatives of isobutyric aldoxime. In this way the author has obtained the methoxy-, ethoxy- and n-propoxy-derivatives. •

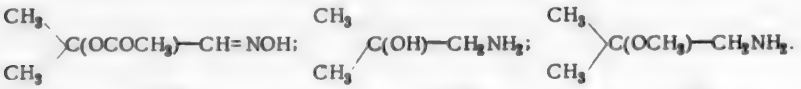
$$(C_4H_8NOCl)_2 \xrightarrow[CaCO_3]{ROH} \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C(OR)\!-\!CH\!=\!NOH,$$ where R = $CH_3$– (IV), $C_2H_5$– (V), n-$C_3H_7$– (VI).

• Recently a patent [4] was published for the derivation of alkoxyisobutyraldoximes (IV), (V) and (VI) by an analogous method. The author had the opportunity of becoming acquainted with it only in the autumn of 1951, when his work had already been completed.

Compounds (III) and (IV) represent viscous liquids (IV) and (V) – crystalline bodies.

Upon reaction of (I) with potassium acetate in glacial acetic acid solution, the acetoxyderivative (VII) was obtained.

Products (III), (IV) and (V) were hydrogenated on Raney nickel to the corresponding amines (VIII), (IX) and (X):

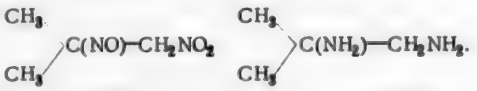


(VII) (VIII) (IX)

Through dehydration of (VIII) with the aid of sulfuric acid, the unsaturated amine (XI) was obtained:

(X) (XI)

The nitrosonitrocompound (XII) which was formed as a by-product upon synthesis of (I) was likewise hydrogenated to the diamine (XIII):



(XII) (XIII)

As a rule compounds (III) through (VII) are obtained with yields 50-60% of the theoretical.

Having in mind the ease of preparation of the nitrosochloride of isobutylene (yields up to 70%), we assume that the above-indicated reactions may be of interest from the preparative viewpoint.

## EXPERIMENTAL

(With the participation of A. N. Shirshova)

Synthesis of Nitrosylsulfuric Acid and Nitrosyl Chloride. The nitrosylsulfuric acid, obtained from nitrogen oxides and sulfuric acid as has been described in the preceding article, was placed in a wide-necked flask with part of the mother liquor, into which flask was introduced a tube ending with glass filter No. 1. Dry air was sucked through the homogeneous liquid mass of nitrosylsulfuric acid for a few hours, while heating on a water bath, to remove oxides of nitrogen. After cooling of the solution, the precipitated nitrosylsulfuric acid crystals were separated from the mother liquor and used to obtain the nitrosyl chloride, as has been shown earlier [3].

Isobutylene Synthesis. Isobutylene was obtained from trimethylcarbinol by dehydration with sulfuric acid [5], and mainly by dehydration of isobutyl alcohol over activated aluminum oxide.

Synthesis of α-Chlorisobutyric Aldoxime Dimer (I). The isobutylene, and then with stirring, the nitrosyl chloride, were introduced at –15° into two large test tubes containing absolute ether, and placed in a Dewar flask with cooling mixture. Within a few minutes after introduction of the nitrosyl chloride the formation of small crystals in the tubes became noticeable, and after 2 hours the reaction mixture from the precipitated crystals solidified. The temperature within the test tubes did not go above minus 12°. Everything was left overnight. 16 hours later the temperature in the test tubes was minus 10°. The crystals were filtered off by vacuum from the blue liquid, and washed with cooled ether until the sky-blue tint disappeared. After removal of the ether residue in a vacuum dessicator – shiny white crystals, with m.p. 98-99°. The first test tube was filled with 72 g of ether, 25 g of isobutylene, 35 g of nitrosyl chloride (29.2 g being required). 39.2 g of crystals was obtained, the yield based upon isobutylene was 72.3% of theoretical. The second test tube was filled with 68 g of ether, 30 g of isobutylene, 31 g of nitrosyl chloride (35 g being required). 34.7 g of crystals was obtained, the yield based upon nitrosyl chloride was 60.3% of the theoretical. After one recrystallization from gasoline (b.p. 60-80°) – long needles, m.p. 103-104°.

Upon distillation of the blue liquid in vacuo, the fraction with b.p. 68-70° at 19 mm was separated – the dark blue liquid presently solidifying into a mass of colorless crystals with m.p. 80-82°. After recrystallization from benzene the m.p. was 82-83°.

0.1281 g substance: 23.7 ml $N_2$ (19°, 752 mm). Found %: N 21.24. $C_4H_9O_3N_2$. Calculated %: N 21.21.

The crystals with m.p. 82-83° corresponded to 1-nitro-2-nitroso-2-methylpropane (XII) [6], according to analysis and properties. The substance (1.5 g) was hydrogenated in an alcoholic solution of Raney nickel. In 4 hours 923 ml of hydrogen was absorbed, 1374 ml of hydrogen (at 22° and 775 mm) being required. After removal of the catalyst, the alcoholic solution was acidified with hydrochloric acid, the alcohol evaporated, and the salt residue recrystallized from alcohol. 0.15 g of chlorohydrate (XII) crystals, with m.p. 292-295°, was obtained. According to the literature data [7], m.p. is 303°.

0.0628 g substance: 9.9 ml $N_2$ (25°, 752 mm). Found %: N 17.67. $C_4H_{12}N_2 \cdot 2HCl$. Calculated %: N 17.36.

Synthesis of α-Hydroxyisobutyric Aldoxime (III). A flask equipped with thermometer, stirrer and reflux condenser, the upper end of which was connected to a trap for $CO_2$ (50% KOH solution) was filled with 180 ml of water, 30 g of finely pulverized and sifted calcium carbonate and 15 g of (I) with m.p. 102.5-103°. The crystals of (I), when the flask was heated, transformed into greenish curd-drops, and at a liquid temperature of about 80°, reaction with the calcium carbonate with $CO_2$ evolution began continuing without further heating, and with the evolution of heat. When the curds had disappeared and the $CO_2$ had ceased to evolve, the yellow liquid was heated to boiling. The whole experiment lasted not more than one hour. 2.69 g of carbon dioxide was evolved, 2.71 g being the theoretical. The solution was separated from the calcium carbonate precipitate and was treated with ether on a reflux for 25-30 hours. From the ether extract, after distilling off the ether and then distilling the residue, a fraction with b.p. 95-97.5° at 10 mm was obtained with a weight of 8.13 g. The yield was 64% of the theoretical. The colorless viscous liquid dissolved readily in water, alcohol, ether, poorly in benzene.

For the α-hydroxyisobutyric aldoxime fraction with b.p. 83-83.5° at 3 mm, which was obtained in one of the experiments, there was found:

$d_{20}^{20}$ 1.0675; $d_4^{20}$ 1.0655; $n_D^{20}$ 1.4625; $MR_D$ 26.63; Calculated 26.40.

0.1458 g substance: 16.7 ml $N_2$ (17°, 758.2 mm). Found %: N 13.38. $C_4H_9O_2N$. Calculated %: N 13.57.

The literature data for the α-hydroxyisobutyric aldoxime [8]: b.p. 110° at 19 mm.

Synthesis of α-Methoxyisobutyric Aldoxime (IV). 10 g of (I), 20 g of finely-ground calcium carbonate in 40 ml of methanol was stirred for one hour while heating to boiling. Completion of reaction was determined by cessation of carbon dioxide evolution. 1.7 g of $CO_2$ was evolved, 1.78 g should have been evolved. After removal of the calcium carbonate, and distilling off of the alcohol, the residue was treated with ether to separate (IV) from the calcium chloride, the ether was distilled off, and the residue redistilled in vacuo. 6 g (63% of the theoretical) of the substance with b.p. 83-85° at 15 mm was obtained, which crystallized in the condenser. M.p. 39-40°. After recrystallization from petroleum ether with freezing, needle-like crystals with m.p. 43-44° were obtained. They dissolved readily in water and in the usual organic solvents. Molecular weight determination pointed to association of the compound.

0.2639 g substance: 16.27 g benzene: Δt 0.435°. 0.2287 g substance: 16.05 g benzene: Δt 0.395°. Found: M 193.2, 187.0. 0.0834 g substance: 18.4 ml $CH_4$ (17°, 766 mm). 0.0723 g substance: 15.6 ml $CH_4$ (18°, 766 mm). Found %: active H 0.93, 0.90. $C_5H_{11}O_2N$. Calculated %: active H 0.95; M 117.1.

Synthesis of α-Ethoxyisobutyric Aldoxime (V). By a procedure analogous to that described in the preceding experiment the ethoxy derivative with b.p. 64-65.5° at 4 mm was obtained. The odor was peculiar, though not unpleasant. The substance was soluble in water and in the usual organic solvents; upon filling a pycnometer, it crystallized into long, dagger-like crystals. The crystals were pressed out on filter paper. M.p. 38-40°.

$d_4^{40}$ 0.9464; $n_D^{40}$ 1.4323; $MR_D$ 35.97; calculated 35.75.

0.1240 g substance: 0.2220 g AgI (Zeitzel). Found %: $OC_2H_5$ 34.36. $C_6H_{13}O_2N$. Calculated %: $OC_2H_5$ 34.35.

Synthesis of α-n-Propoxyisobutyric Aldoxime (VI). 24.3 g of (I) 82 g of n-propyl alcohol and 40 g of calcium carbonate were taken. Experimental conditions were the same as in the preceding two cases. Reaction started at 70° and spontaneously continued with heat evolution (up to 85°). After 2 hours of heating to boiling, followed by the usual treatment, and three distillations, fractions at 83-85° and at 85-86°, at 8 mm, were separated, with weights of 2.39 and 9.05 g respectively. The yield for the two fractions was 39.5%. The fraction with b.p. 85-86 at 8 mm was a colorless, viscous liquid, with a faint odor resembling the methoxy- and ethoxy-derivatives.

$d_{20}^{20}$ 0.9436; $d_4^{20}$ 0.9420; $n_D^{20}$ 1.4414; $MR_D$ 40.70; Calculated 40.37.

0.1342 g substance: 11.6 ml $N_2$ (18°, 749 mm). 0.1206 g substance: 10.1 ml $N_2$ (17°, 748 mm). Found %: N 9.85, 9.55. $C_7H_{15}O_2N$. Calculated %: N 9.64.

Synthesis of α-Acetoxyisobutyric Aldoxime (VII). 60 g (0.49 mole) of isobutylene nitrosochloride was dissolved with gentle heating in 250 ml of glacial acetic acid. To the green solution was added 50 g (0.51 mole) of anhydrous potassium acetate in 200 ml of glacial acetic acid solution. The mixture was stirred while heating at a temperature of 60°, the heating then discontinued, while the temperature rose spontaneously to 73°. Potassium chloride precipitated in large amount. The reaction mass was stirred for an additional hour while heating to 80-85°. On the following day the yellow transparent liquid was separated from the potassium chloride precipitate, washed with acetic acid, and the dried precipitate weighed 33.65 g – 0.45 mole. The acetic acid was distilled off in vacuo from the reaction products at 35° and 16 mm.

Upon distillation of the residue a fraction with b.p. 89-92° at 3 mm was obtained, weighing 37.9 g (yield 53% of theoretical). Repeated distillation of this fraction gave a fraction with b.p. 91-92° at 6 mm. Viscous, colorless liquid almost without odor. Soluble in water, alcohol, ether, benzene, acetic acid, carbon tetrachloride; insoluble in gasoline.

$d_4^{20}$ 1.0757; $n_D^{20}$ 1.4503; $MR_D$ 36.28; Calculated 35.76.

0.2768 g substance: 23.3 ml $N_2$ (21°, 750 mm). Found %: N 9.56. $C_6H_{11}O_3N$. Calculated %: N 9.65.

Synthesis of 1-Amino-2-methoxy-2-methylpropane (IX). 6.4 g of (IV) in 70 ml of distilled alcohol solution was hydrogenated with Raney nickel under the usual conditions. 2.174 ml of hydrogen was absorbed, 2.448 ml being required. After separation of the nickel the solution was neutralized with hydrochloric acid. 5.2 g of the amine hydrochloride, with m.p. 112-113° was obtained by the usual procedure, and purified by repeated precipitation by ether from the alcohol solution. Yield 68.2%.

0.1069 g substance: 0.1118 g AgCl. Found %: Cl 25.87. $C_5H_{13}ON \cdot HCl$. Calculated %: Cl 25.42.

The free base (IX) was separated from the salt by the action of 12% caustic potash solution with subsequent distillation. The distillate was saturated with solid caustic potash, the amine layer separated, and extracted with ether. After drying with caustic potash, the ether was removed and upon redistillation the amine (IX) fraction with b.p. 121.5-122.5° at 753 mm was obtained. It was a colorless, transparent liquid with ammoniacal odor. It was soluble in water and the usual organic solvents.

$d_4^{20}$ 0.8677; $n_D^{20}$ 1.4210; $MR_D$ 30.14; Calculated %: 30.35.

0.1662 g substance: 19.4 ml $N_2$ (19°, 747 mm). Found %: N 13.32. $C_5H_{13}ON$. Calculated %: N 13.56.

Synthesis of 1-Amino-2-ethoxy-2-methylpropane (X). 27.25 g of (V) in 230 ml of absolute alcohol was hydrogenated with Raney nickel in a rotating steel autoclave at a pressure of 110 atmospheres and a temperature of 18°. After distillation through a fractionating column with 10 theoretical plates, the following amine fractions were obtained (at 755 mm): 1) 131-132 1.3 g, $n_D^{20}$ 1.4182; 2) 132-133° 14.3 g. The yield for the 132-133° fraction was 59%. Colorless, transparent liquid with amine odor. Soluble in water and the usual organic solvents.

$d_4^{20}$ 0.8497; $n_D^{20}$ 1.4189; $MR_D$ 34.82; Calculated 34.97.

0.1479 g substance: 16.2 ml $N_2$ (19°, 739.5 mm). 0.1414 g substance: 15.1 ml $N_2$ (20°, 743 mm). Found %: N 12.35, 12.05. $C_6H_{15}ON$. Calculated %: N 11.95.

Synthesis of 1-Amino-2-methylpropanol-2 (VIII). 34 g of the oxime (III) in 200 ml of alcohol solution was hydrogenated in the presence of Raney nickel in a rotating steel autoclave at the pressure of 80 atmospheres and 100° temperature. From the hydrogenation products 15.5 g of 1-amino-2-methylpropanol-2 was separated with a b.p. of 149-150° at 755mm. Yield was 53% of the theoretical. In separate experiments the yield of amino-alcohol was higher than 60%. For the fraction with b.p. 149-150° at 755 mm:

$d_4^{18}$ 0.9323; $n_D^{18}$ 1.4460; $MR_D$ 25.50; Calculated 25.62.

For the fraction with b.p. 150-150.5° at 762 mm, obtained in a separate experiment:

$d_{20}^{20}$ 0.9294; $d_4^{20}$ 0.9278; $n_D^{20}$ 1.4452; $MR_D$ 25.58; Calculated 25.62.

0.0869 g substance: 12.1 ml $N_2$ (22°, 752 mm). 0.1133 g substance: 15.8 ml $N_2$ (20.5°, 749 mm). Found %: N 15.62, 15.68. $C_4H_{11}ON$. Calculated %: N 15.71.

Literature data [9] b.p. 150.5-151.5° at 762 mm, $d_0^0$ 0.9500, $d_0^{14}$ 0.9389.

Synthesis of 1-Amino-2-methylpropene-2 (XI). 15.1 g of distillate of ammoniacal odor was obtained from 23.3 g of the aminoalcohol by dehydration with sulfuric acid under the conditions indicated in the literature [10], from which 8.75 g of substance was isolated after drying and distilling, boiling mainly at 83-84°. Upon subsequent distillation, two fractions of the amine were obtained (at 763 mm): 1) 72-82° 2.03 g and 2) 82-85° 5.59 g.

From the 72-82° fraction the hydrochloride salt was obtained, After two precipitations with ether, the b.p. was 179.5-180.5°.

Picrate – long, narrow, flat flakes (up to 2 centimeters in length) with m.p. 201-201.5° (from absolute alcohol).

The fraction with b.p. 82-85° at 763 mm was a colorless transparent liquid with a specific (but not ammoniacal) odor. Insoluble in water. Upon heating with alkali a strong ammonia odor appeared; the same also occurred after several days of storage.

Hydrogen Chloride Salt, purified by reprecipitation from alcohol solution by ether, had a m.p. of 185.5-186.5°.

0.0796 g substance: 0.1042 g AgCl. 0.0846 g substance: 0.1114 g AgCl. Found %: Cl 32.39, 32.58. $C_4H_9N \cdot HCl$. Calculated %: Cl 32.96.

Picrate – m.p. 201.5-202° (not recrystallized).

0.1002 g substance: 16 ml $N_2$ (18°, 768 mm). Found %: N 18.63. $C_6H_2(NO_2)_3OH \cdot C_4H_9N$. Calculated %: N 18.66.

The unsaturated amine (XI) content in the fraction 82-85° was determined by titration (using bromophenol blue).

0.1088 g substance: 11.1 ml 0.1 N $H_2SO_4$. 0.0932 g substance: 9.5 ml 0.1 N $H_2SO_4$. Found %: amine 72.6, 72.5.

The yield of amine (XI) upon dehydration was about 33%.

The fraction with b.p. 82-85° was twice redistilled, and each time was dried over NaOH beforehand.

Fractions obtained (at 759 mm): 1) 73.5-77° 0.2 g, $n_D^{20}$ 1.4282; 2) 77-79° 1.42 g.

The 77-79° fraction at 759 mm was a colorless, highly mobile, liquid with a strong ammoniacal odor:

$d_{20}^{20}$ 0.7838; $d_4^{20}$ 0.7827; $n_D^{20}$ 1.4300;* $MR_D$ 23.47. $C_4H_9N$. Calculated 23.63.

Literature data [10]: b.p. 76-77.7° at 746 mm, $n_D^{20}$ 1.4312.

## SUMMARY

1. The oximes of α-hydroxyisobutyric aldehyde, α-methoxyisobutyric aldehyde, α-ethoxyisobutyric aldehyde, α-n-propoxyisobutyric aldehyde and α-acetoxyisobutyric aldehyde were obtained from the chloronitrosocompound of isobutylene upon reaction with water and with alcohols.

2. 1-Amino-2-methylpropanol-2, its methyl and ethyl esters, and 1,2-diamino-2-methylpropane were obtained upon hydrogenation of the oximes of α-hydroxyisobutyric aldehyde, α-methoxyisobutyric aldehyde, α-ethoxyisobutyric aldehyde, and 1-nitro-2-nitroso-2-methylpropane, respectively.

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* It is of interest to note that after 2-3 minutes the refractive index was already 1.4293, which indicated a ready change of the amine in air. ** See Consultants Bureau translation page 607 . *** See Consultants Bureau translation page 2167.

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# ACYL PEROXIDES. DICAPRYL PEROXIDE

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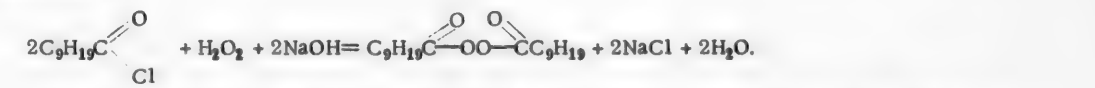
Acyl peroxide compounds are of interest from many points of view. On the basis of the reaction discovered by N. A. Prilezhaev, acyl hydroperoxides have been employed for determination of structure and for the quantitative analysis of unsaturated compounds [1,2,3]. Lately the diacyl peroxides have found application in organic synthesis as alkylating agents, or to produce many other interesting transformations [4].

At the same time the number of acyl peroxide compounds which have been isolated and determined up to the present time is relatively small, and it should be noted here that many of them have not been isolated in sufficiently pure form.

Among the acyl hydroperoxides (of per acids) have been described: performic, peracetic, perpropionic, perbutyric, percaproic, perbenzoic, and a series of others (in this number are also derivatives of the dicarboxylic acids – of succinic, glutaric, phthalic, camphoric, oxalic and terephthalic – possessing one hydroperoxide group), obtained chiefly by reaction of hydrogen peroxide (concentrated or dilute) with the appropriate acids, anhydrides or chloroanhydrides of the acids (see [5] and others) in the presence of small quantities of sulfuric acid or alkali,

Of the diacyl peroxides there are known the peroxides of diacetyl, dichloroacetyl, dipropionyl, dibutyryl, diisovaleryl, dicapryl, dinitrobenzoyl, acetylbenzoyl and some others, obtained principally by interaction of the anhydrides or the chloroanhydrides of the corresponding acids with hydrogen peroxide (in the presence of alkaline reagents with the alkali or alkaline earth salts (see [6]) and others).

The authors carried out acylation of hydrogen peroxide by capric acid chloroanhydride. With selected ratio – 2 moles of chloroanhydride per 1 mole of hydrogen peroxide – the dicapronyl peroxide results according to the reaction:



$$2C_9H_{19}C(=O)Cl + H_2O_2 + 2NaOH = C_9H_{19}C(=O)OOC(=O)C_9H_{19} + 2NaCl + 2H_2O.$$

The dicapryl peroxide (or didecanoyl according to the Geneva nomenclature) is in the form of a crystalline substance with m.p. +41°. It has relatively small oxidizing properties: iodine separates very slowly from acidified potassium iodide solution. Dicapryl peroxide is soluble in organic solvents (ethyl ether, alcohols, ketones, hydrocarbons) but is insoluble in water.

## EXPERIMENTAL

10.2 g of capric acid chloroanhydride (obtained from pure capric acid with a m.p. of 31.4, according to the method of Kraft and Koenig [7] was added dropwise, while stirring rapidly, to a mixture of 35 ml of 3% aqueous hydrogen peroxide and 44 ml of 5% sodium hydroxide solution at room temperature. The mixture was allowed to stand for 24 hours. Colorless crystals of the peroxide (displaying a laminar structure under the microscope) precipitated after this lapse of time, were filtered off, and washed with water. Yield was 5.6 g or 61.3% of the theoretical.

After triple recrystallizations from ethanol, the peroxide melted at +41°. It gave qualitative reactions for active oxygen – iodine separated from potassium iodide solution, upon heating thiocyanate solution was slowly colored, but it did not react with lead tetra-acetate, the indicator for the absence of hydroperoxide group.

Elementary analysis results for the dicapryl peroxide (carried out according to the semimicro method of Pregl):

0.0322 g substance: 0.0823 g $CO_2$; 0.0332 g $H_2O$. 0.0408 g substance: 0.1050 g $CO_2$, 0.0427 g $H_2O$. Found %: C 69.75, 70.20; H 11.27, 11.72. $C_{20}H_{38}O_4$. Calculated %: C 70.17; H 11.20.

0.2235 g substance: 22.04 g benzene: $\Delta t$ 0.150°. Found: M 346.0. $C_{20}H_{38}O_4$. Calculated: M 342.5.

The active oxygen content was determined by the iodometric method in glacial acetic acid solution: titration after 24 hours [8]:

0.0456 g substance: 2.65 ml 0.1 N $Na_2S_2O_3$. 0.0468 g substance: 2.7 ml 0.1 N $Na_2S_2O_3$. Found %: active O 4.65, 4.61. $C_{20}H_{32}O_4$. Calculated %: active O 4.67.

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# ADDITION OF PHOSPHONACETIC ESTER AND ITS HOMOLOGS TO UNSATURATED ELECTROPHILIC REAGENTS

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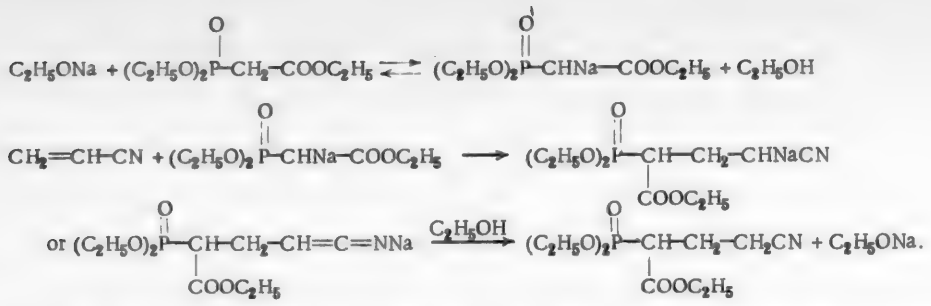
A. E. Arbuzov and Dunin [1] synthesized for the first time in 1914 the ethyl ester of phosphonacetic acid by reaction of the ethyl ester of bromoacetic acid with the full ethyl ester of phosphorous acid. In an analogous manner certain representatives of the phosphonocarboxylic acid series were likewise synthesized by them: the ethyl esters of phosphonoformic, α- and β-phosphonopropionic and phosphonobutyric acids. In 1924 Nylen [2] synthesized the phosphonoacetic ester by reaction of chloroacetic ester with sodium diethylphosphite in ether solution. A. E. Arbuzov and Kamai [3] later improved this method considerably, and demonstrated that substitution of ether by ethanol brought the yield of phosphonoacetic ester up to 95% of the theoretical. In 1929 A. E. Arbuzov and Razumov [4] synthesized the homolog of phosphonoacetic ester – the ethyl ester of α-diethylphosphonopropionic acid in 45% yield by the reaction of methyl iodide on the sodium derivative of phosphonoacetic ester. It was established at the same time that there is formed considerable quantity of the monosodium salt of α-phosphonopropionic acid ester and of ethyl iodide along with the normal reaction product. Such an abnormal reaction course was explained on the grounds that the sodium derivative of the phosphonoacetic ester may exist in two tautomeric forms. With the potassium phosphonoacetic ester the reaction proceeds only according to the normal scheme: the phosphonopropionic ester yield reaches 85%. A. E. Arbuzov and Razumov [5] further demonstrated the tautomerism of phosphonoacetic ester in the case of the methyl iodide reaction with the sodium derivative of the ethyl ester of diisobutylphosphonoacetic ester. Lately Chavene [6], employing the method described in the work of Arbuzov and Razumov, synthesized α-diethylphosphono-n-hexyl-acetic ester.

From a review of the literature data cited it can be seen already that phosphonoacetic ester appears to be a substance of considerable interest, presenting great theoretical interest for the study of the tautomerism phenomenon and for the purpose of synthesis of organophosphorous compounds.

As has already been indicated, it was established through the investigations of A. E. Arbuzov and Razumov that there are mobile hydrogen atoms in phosphonoacetic ester, which are replaceable by the alkali metals in a manner corresponding to acetoacetic, malonic and cyanacetic esters. It seemed probable to us that phosphonoacetic ester can display an analogy with the indicated esters in other reactions also: addition reactions, reactions with aldehydes and ketones, and so forth, which are likewise connected with the mobility of the hydrogen atoms of the methylene group. Having in mind the considerable interest of similar reactions, completely uninvestigated up to the present time, the authors have undertaken in the present work a study of the addition reactions of phosphonacetic ester to certain unsaturated electrophilic reagents: the nitrole of acrylic acid, the methyl esters of acrylic, methacrylic and maleic acids, the ethyl ester of cinnamic acid, the unsaturated ketones of benzal-, furfural-acetone and mesityl oxide.

In a majority of the cases, reactions were carried out according to the procedure described by one of us for the addition reactions of dialkyl phosphorous acids to unsaturated compounds [7]. Preliminary experiments carried out by the authors have shown that phosphonacetic ester, in the presence of sodium ethylate, adds to the majority of unsaturated compounds used for this purpose, with more or less ease. The addition of phosphonacetic ester to acrylic acid nitrile in the presence of a small quantity of sodium ethylate proceeds vigorously, accompanied by a heat of reaction evolution with partial resinification of the reaction mixture. Attempts to distill fractionally result in complete resinification. Satisfactory results were obtained by conducting the reaction in ethanol solution. The products from the addition of the phosphonacetic ester to one or two molecules of acrylonitrile were isolated with a general yield of 50% of theory.



Reaction between the phosphonacetic ester and methyl acrylate in the presence of sodium ethylate also proceeds quite vigorously with large heat evolution from the reaction mixture. The yield of addition product—the methyl ethyl ester of α-diethylphosphonglutaric acid—was 41%. Similarly, for the course of reaction between methyl methacrylate and the ethyl ester of cinnamic acid, there were obtained: the methylethyl ester of α-methyl-α'-diethylphosphonglutaric acid in 45% yield, and the diethyl ester of α-diethylphosphon-β-phenylglutaric acid. To carry out the latter reaction, which under normal conditions proceeded only very slowly, the reaction mixture was heated several hours on a water bath. The esters obtained were in the form of colorless, very viscous liquids, surface-active with respect to water.

Phosphonacetic ester addition to the methyl ester of maleic acid proceeded with the same difficulty. Regardless of the prolonged heating of the reaction mixture, the addition product—the dimethyl ester of α-diethylphosphon-α,β,γ-propanetricarboxylic acid—was obtained only in 12% yield.

The addition of phosphonacetic ester to benzalacetone in the presence of sodium ethylate proceeds easily; under more rigorous conditions the addition of furfuralacetone proceeds. The addition of phosphonacetic ester to mesityl oxide failed to go even when the reaction mixture was heated to 250°. Apparently, in the last instance, the effect of spatial hindrance and the electrophilic decrease of the carbon atom of the unsaturated ketone due to the presence of the two attached methyl groups, is evident.

It was of further interest to the authors to study the addition of phosphonacetic ester homologs to certain unsaturated compounds. For this purpose n-butylphosphonacetic ester was synthesized and its addition to acrylic acid nitrile, methylacrylate and methylmethacrylate was carried out. In contrast to phosphonacetic ester, the n-butylphosphonacetic ester adds quite smoothly to acrylonitrile in the absence of solvents, with moderate heat evolution. The addition product—the ethyl ester of α-(β-cyanethyl)-α-diethylphosphoncapric acid was obtained in 84% yield. Similar results were likewise obtained with the methylphosphonacetic acid ester. Addition products of n-butylphosphonacetic ester to methylacrylate and to methylmethacrylate were obtained in high yields (of the order 80-85%). All products synthesized were in the form of thick, colorless liquids, surface-active with respect to water.

## EXPERIMENTAL

Addition of Phosphonacetic Ester to Acrylic Acid Nitrile. 7.5 g of phosphonacetic ester and 3.45 g of acrylic acid nitrile were dissolved in 20 ml of absolute ethanol. The flask with the reaction mixture was connected to a reflux condenser, and then a saturated sodium ethylate solution in ethanol slowly added dropwise. During the course of reaction the flask was cooled with running water, since reaction was accompanied by considerable heat evolution, resulting in boiling of the alcohol if not cooled sufficiently. After completion of reaction, the alcohol was distilled off and the residue fractionally distilled in vacuo. Separated were:

1) a small amount of original phosphonacetic ester;

2) 2.5 g of the ethyl ester of diethylphosphon-(α-cyanethyl)-acetic acid with b.p. 185-186° (4 mm); $n_D^{20}$ 1.4470; $d_4^{20}$ 1.1065;

0.1860 g substance: 32.98 ml NaOH (T 0.0225). Found %: P 11.05. $C_{11}H_{20}O_5NP$. Calculated %: P 11.17;

3) 3 g of diethylphosphon-di-(β-cyanethyl)-acetic acid ethyl ester with b.p. 230-231° (5 mm); $n_D^{20}$ 1.4580; $d_4^{20}$ 1.1307;

0.2070 g substance: 32.85 ml NaOH (T 0.02477). Found %: P 8.64. $C_{14}H_{23}O_5N_2P$. Calculated %: P 9.04.

Addition of the Phosphonacetic Ester to the Methyl Ester of Acrylic Acid. A saturated sodium ethylate solution was slowly added dropwise to a mixture of 10.4 g of phosphophonacetic ester and 4 g of methylacrylate. The reaction was accompanied by considerable heat evolution. In all, 10 drops of ethylate were added. After standing for a short time the reaction mixture was fractionally distilled. After distilling off the unreacted phosphonacetic ester, 5.85 g of the mixed methylethyl ester of $\alpha$-diethylphosphonglutaric acid with b.p. 209° (4 mm) was obtained: $n_D^{20}$ 1.4510; $d_4^{20}$ 1.1474;

0.1320 g substance: 21.38 ml NaOH (T 0.0225). Found %: P 10.08. $C_{12}H_{23}O_7P$. Calculated %: P 10.00.

Addition of Phosphonacetic Ester to the Methyl Ester of Methacrylic Acid. The reaction was carried out by heating 13.2 g of phosphonacetic ester with 6.7 g of methylmethacrylate in the presence of sodium ethylate on a water bath; dropwise addition of the ethylate was likewise carried out while heating. The color of the reaction mixture by the end of the heating period had changed from pink to dark-red. As the result of a double distillation of the reaction mixture, 7.69 g of the methylethyl ester of $\alpha$-methyl-$d$-diethylphosphonglutaric acid was isolated, b.p. 199-201° (13 mm); $n_D^{20}$ 1.4450; $d_4^{20}$ 1.1172;

0.1269 g substance: 20.1 ml NaOH (T 0.0225). Found %: P 9.86. $C_{13}H_{25}O_7P$. Calculated %: P 9.57.

Addition of Phosphonacetic Ester to Ethyl Cinnamate. Sodium ethylate solution was added dropwise to a mixture of 5 g of freshly distilled ethyl cinnamate and 7 g of phosphonacetic ester. Heat evolution was not observed. The reaction mixture was heated for 5 hours on a boiling water bath after the addition of about 1 ml of the ethylate solution. As the result of distillation in vacuo, 3 g of $\alpha$-diethylphosphon-$\beta$-phenylglutaric acid diethyl ester was isolated with b.p. 190-192° (2 mm); $n_D^{20}$ 1.4740; $d_4^{20}$ 1.1272;

0.1967 g substance: 25.06 ml NaOH (T 0.0225). Found %: P 7.93. $C_{19}H_{30}O_7P$. Calculated %: P 7.76.

Addition of Phosphonacetic Ester to the Dimethyl Ester of Maleic Acid. To a mixture of 8.2 g of phosphonacetic ester and 5.9 g of the methyl ester of maleic acid there was added about 2 ml of saturated sodium ethylate solution. There was no evolution of heat. After 2 hours of heating, the reaction mixture was distilled in vacuo on a water bath. 1.7 g of $\alpha$-diethylphosphon-$\alpha$-$\beta$-$\gamma$-propanetricarboxylic acid dimethyl ester was obtained with b.p. 173-175° (3 mm); $n_D^{20}$ 1.4395; $d_4^{20}$ 1.1730.

0.2376 g substance: 34.0 ml NaOH (T 0.0225). Found %: P 8.91. $C_{14}H_{25}O_7P$. Calculated %: P 8.42.

Addition of Phosphonacetic Ester to Benzalacetone. Sodium ethylate solution was added dropwise to a mixture of 6.6 g of benzalacetone and 10 g of phosphonacetic ester. Strong heat evolution was observed. After heating for a short time on the water bath, the reaction mixture was distilled in vacuo. 8 g of $\alpha$-diethylphosphono-$\beta$-phenyl-$\gamma$-acetobutyric acid ethyl ester was obtained with b.p. 207-210° (6 mm); $n_D^{20}$ 1.5019; $d_4^{20}$ 1.1356.

0.1203 g substance: 16.46 ml NaOH (T 0.0225). Found %: P 8.52. $C_{18}H_{27}O_6P$. Calculated %: P 8.4.

Addition of Phosphonacetic Ester to Furfuralacetone. The addition reaction failed to go at room temperature and when heated on a water bath. 10 g of phosphonacetic ester, 5 g of furfuralacetone and 3 ml of saturated sodium ethylate solution were heated in a sealed tube at 130-135° for 10 hours. The color of the solution changed from light-yellow to dark-brown. As a result of fractional distillation of the reaction mixture, the initial furfuralacetone, and phosphonacetic ester were recovered and 1.5 g of the addition product—the ethyl ester of $\alpha$-diethylphosphon-$\beta$-furil-$\gamma$-acetobutyric acid with b.p. 138-139° (3 mm); $n_D^{20}$ 1.4490; $d_4^{20}$ 1.109.

Found %: P 8.50. $C_{16}H_{25}O_7P$. Calculated %: P 8.61.

The product obtained was a brown-colored liquid; the vapors were bright yellow in color. Upon standing it gradually resinified.

Synthesis of n-Butylphosphonacetic Ester. 150 ml of absolute ether and 3.4 g of finely cut sodium were placed in a three-necked round-bottomed flask, equipped with reflux condenser, stirrer and dropping funnel. Then 35 g of phosphonic ester was added dropwise with stirring. The reaction mixture was stirred for 1.5 hours almost to the complete disappearance of the sodium. The small amount of sodium which did not enter into reaction was removed from the reaction mixture with the aid of a long glass needle. 24 g of n-butyl bromide was then gradually added to the reaction mixture, and the mixture was then heated on a water bath for 2.5 hours. The colloidal sodium bromide precipitated when the reaction mixture was boiled for a short time with activated carbon. After filtering off the precipitate, and distilling off the ether, the residue was fractionally distilled from an Arbuzov flask. 21.2 g of n-butyl phosphonacetic ester was obtained with b.p. 154-156° (9 mm); $n_D^{20}$ 1.4360; $d_4^{20}$ 1.0406.

0.1628 g substance: 28.69 ml NaOH (T 0.0225). Found %: P 10.98. $C_{12}H_{25}O_5P$. Calculated %: P 11.07.

Addition of n-Butylphosphonacetic Ester to Acrylic Acid Nitrile. 4 drops of saturated sodium ethylate solution in ethanol was gradually added, with ice cooling, to a mixture of 6 g of n-butylphosphonacetic ester and 1.5 g of acrylic acid nitrile. The reaction proceeded with considerable heat evolution from the mixture. There was no resinification. After a half-hour standing at room temperature the reaction mixture was distilled in vacuo. 5 g of α-(β-cyanethyl-)-α-diethylphosphonocaproic acid ethyl ester was obtained with b.p. 186-187° (2 mm); $n_D^{20}$ 1.4500; $d_4^{20}$ 1.0641.

0.1492 g substance: 22.46 ml NaOH (T 0.0225). Found %: P 9.36. $C_{15}H_{28}O_5NP$. Calculated %: P 9.33.

Addition of Methylphosphonacetic Ester to Acrylic Acid Nitrile. From 5 g of methylphosphonacetic ester [b.p. 126° (5 mm)] and 3 g of acrylic acid nitrile, under conditions similar to those described in the preceding experiment, there was obtained 3.6 g of the ethyl ester of diethylphosphon-(β-cyanethyl-)-acetic acid, with b.p. 176-178° (5 mm); $n_D^{20}$ 1.4430; $d_4^{20}$ 1.0960.

0.2283 g substance: 36.84 ml NaOH (T 0.0225). Found %: P 10.06. $C_{12}H_{22}O_5NP$. Calculated %: P 10.65.

Addition of n-Butylphosphonacetic Ester to the Methyl Esters of Acrylic and of Methacrylic Acids. Experiment I. The reaction was carried out with 7 g of n-butylphosphonacetic ester and 2 g of the methyl ester of acrylic acid. Considerable heat evolution was observed. 7.2 g of the methyl ethyl ester of α-n-butyl-α-diethylphosphonglutaric acid with b.p. 179-181° (3 mm) was obtained; $n_D^{20}$ 1.4510; $d_4^{20}$ 1.1002.

0.1164 g substance: 16.3 ml NaOH (T 0.0225). Found %: P 8.72. $C_{16}H_{31}O_7P$. Calculated %: P 8.47.

Experiment II. As the result of reaction between 4 g of n-butylphosphonacetic ester and 1.5 g of methylmethacrylate, there was obtained 4.2 g of the methylethyl ester of α-methyl-α'-n-butyl-α'-diethylphosphonoglutaric acid with b.p. 169-170° (2 mm); $n_D^{20}$ 1.4490; $d_4^{20}$ 1.0818.

0.1945 g substance: 23.89 ml NaOH (T 0.0225). Found %: P 7.65. $C_{17}H_{33}O_7P$. Calculated %: P 8.01.

## SUMMARY

1. It was demonstrated that phosphonacetic ester and its homologs are capable of addition to unsaturated electrophilic reagents in the presence of sodium ethylate: to unsaturated nitriles, ester of acids and to ketones.

2. Addition products of phosphonacetic ester to acrylic acid nitrile, methylacrylate, methylmethacrylate, cinnamic acid ethyl ester, maleic acid methyl ester, benzal- and furfural-acetone, and similarly addition products of n-butylphosphonacetic ester to acrylonitrile, methylacrylate and methylmethacrylate were obtained and characterized.

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# ADDITION OF HYDROGEN BROMIDE TO DIALLYL

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N. Ya. Demyanov [1] was the first to study the addition of HBr to diallyl, who, by passing gaseous hydrogen bromide into cooled diallyl to the point of saturation, obtained the crystalline dibromide – 2,5-dibromhexane, and also an addition product which he did not further examine. Later Grishkevich-Trokhimovsky [2] demonstrated that the liquid product from the addition of HBr to diallyl represents a mixture of dibromhexanes, in which 1,5-dibromhexane predominates, and so HBr addition to diallyl occurs simultaneously according to Markownikoff's rule and in contradiction to the rule at the same time.

The stepwise addition of gaseous hydrogen bromide to diallyl and separation of incomplete addition to one double bond was studied. Upon reaction of diallyl with concentrated hydrochloric acid [3], hydrogen bromide dissolved in glacial acetic acid [10], and with gaseous hydrogen bromide [11], the products of incomplete addition were isolated earlier, and represented 5-chlor-, 5-brom- and 5-iod-hexene-1. On the basis of the preceding investigation, it could be expected that upon addition of gaseous hydrogen bromide to diallyl, the first step of the reaction would result either in the secondary bromide – 5-bromhexene-1 (I), or along with it the primary – 6-bromhexene-1 (II); the latter could occur in this instance if the first stage of HBr addition to the diallyl proceeded in both directions.

(I) $CH_2=CH-CH_2-CH_2-CHBr-CH_3$; (II) $CH_2=CH-CH_2-CH_2-CH_2-CH_2Br$.

The experiments described below indicate that the product of incomplete addition of hydrogen bromide to diallyl results in good yield (about 60% of the theoretical) if gaseous hydrogen bromide is passed into the diallyl, with mechanical stirring, in an amount equal to half of that required for saturation of one double bond. The product obtained in this manner boils over a wide range (137.5-151°), and can be separated into two fractions with b.p. 137.5-138.5° and 150-151° by fractional distillation. Comparing the physical properties of these fractions among themselves, and also with the properties of other unsaturated bromides with the double bond at the end of the chain which are described in the literature, it can be concluded that the fraction with b.p. 150-151° possessing the higher boiling point and higher specific gravity, should represent the primary bromide – 6-bromohexene-1, and the fraction with b.p. 137.5-138.5 – the secondary bromide – 5-bromhexene-1 (see table).

| Substance | Boiling point | $d_4^{20}$ | $n_D^{20}$ |
|---|---|---|---|
| $CH_2=CH-CH_2Br$ [5] | 70–71° | 1.3980 | 1.46545 |
| $CH_2=CH-CH_2-CH_2Br$ [4] | 98.5-99 | 1.3230 | 1.46215 |
| $CH_2=CH-CH_2-CH_2-CH_2Br$ [4] | 126 | 1.2581 | 1.46397 |
| $CH_2=CH-CH_2-CH_2-CH_2-CH_2Br$ | 151 | 1.2169 | 1.4672 |
| $CH_2=CH-CHBr-CH_3$ [6] | 7° (10 mm) | 1.2998 (25°) | 1.4618 |
| $CH_2=CH-CH_2-CH_2-CHBr-CH_3$ | 138 | 1.1997 | 1.4625 |

To confirm that the fraction with b.p. 137.5-138.5° in reality does represent 5-bromohexene-1, this bromide was synthesized by another method which is common for the synthesis of unsaturated bromides, namely – the reaction of phosphorous tribromide, in the presence of pyridine, with hexene-1-ol-5 [4]. Upon comparing their physical constants, both products were found to be identical. The primary character of the bromide with b.p. 150-151° was first of all demonstrated by the fact that when it was reacted with $AgNO_2$, according to V. Meyer, it behaved like a primary halogen derivative forming in the end an orange-red salt solution of nitrolic acid. Furthermore, upon reacting this bromide with sodium acetate in glacial acetic acid, it transformed into the acetate, which, upon saponification, formed an alcohol which differed from its isomeric secondary alcohol, hexene-1-ol-5, by higher constants, and represented hexene-1-ol-6.

| Substance | Boiling point | $d_4^{20}$ | $n_D^{20}$ |
|---|---|---|---|
| $CH_2=CH-CH_2-CH_2-CHOH-CH_3$ | 139° | 0.8390 | 1.4325 |
| $CH_2=CH-CH_2-CH_2-CH_2-CH_2OH$ | 155.5-156 | 0.8453 | 1.4364 |

Moreover, upon reacting the above-boiling bromide with alkali in water-alcohol, it transformed into the previously known ethyl ether of hexene-1-ol-6 $CH_2=CH-CH_2-CH_2-CH_2-CH_2-O-C_2H_5$ [7]. All of these characteristics point to the conclusion that the bromide of b.p. 150-151° represents 6-bromohexene-1.

Thus, in the first step the addition reaction of hydrogen bromide to diallyl proceeds in two possible directions. The second step of the reaction was studied by the example of hydrogen bromide addition to the secondary bromide. It was found at this time that upon reaction of hydrogen bromide with 5-bromohexene-1, under the same conditions that the addition proceeded almost entirely according to Markownikoff's principle, and a mixture of liquid and crystalline 2,5-dibromohexanes resulted.

## EXPERIMENTAL

Diallyl obtained by reacting metallic sodium with allyl iodide [8] and having the following properties: b.p. 56-59°; $d_4^{20}$ 0.6897; $n_D^{20}$ 1.4018, served as the starting substance for the work.

Addition of HBr to Diallyl 164 g (2 moles) of diallyl was placed in a flask equipped with an inlet tube reaching almost to the bottom of the flask, a reflux condenser and a mechanical stirrer. The flask was cooled in a mixture of ice and salt, and 81 g (1 mole) of hydrogen bromide, obtained from bromine, red phosphorus and water, was introduced, with vigorous agitation. The flask was then removed from the cooling mixture and left overnight. On the following day the flask contents were distilled through a Vigreux column, at which time the following resulted on the average:

1) diallyl with b.p. 56-60° – 81 g; 2) fraction with b.p. 130-160° – 129 g; 3) residue – 32.5 g.

The recovered diallyl was again saturated with HBr (1 mole of HBr for 2 moles of diallyl); thus 240 g of diallyl was treated and 309 g of fraction with b.p. 130-160° and 130 g of residue, representing a mixture of dibromohexanes, were obtained. The 130-160° fraction was separated into the following fractions as the result of multiple distillation through a Vigreux column 0.6 meter in height:

I) b.p. 137.5-138.5° at 712 mm – 12.5 g; II) b.p. 138.5-150° – 56 g; III) b.p. 150-151° – 101 g. Total yield was 59% of the theoretical, the 137.5-138.5° fraction had a 26% yield; fraction 150-151° – 21.4%. Fraction I constants: b.p. 138° at 712 mm; $d_4^{20}$ 1.1997; $n_D^{20}$ 1.4625; $MR_D$ 37.39 calculated 37.21.

0.2834 g substance: 0.4583 g $CO_2$; 0.1678 g $H_2O$. 0.2168 g substance: 0.2503 g AgBr (Carius). Found %: C 44.10; H 6.58; Br 49.12. $C_6H_{11}Br$. Calculated %: C 44.17; H 6.75; Br 49.08.

Fraction II constants: b.p. 151 at 712 mm; $d_4^{20}$ 1.2169; $n_D^{20}$ 1.4672; $MR_D$ 37.18; calculated 37.21.

0.3060 g substance: 0.4941 g $CO_2$; 0.1815 g $H_2O$. 0.2826 g substance: 0.3263 g AgBr (Carius). Found %: C 44.03; H 6.59; Br 49.18. $C_6H_{11}Br$. Calculated %: C 44.17; H 6.75; Br 49.08.

Reaction of $PBr_3$ with Hexene-1-ol-5. 35 g (0.13 mole) of phosphorous tribromide was placed in a Wurtz flask equipped with dropping funnel and condenser, and then with constant shaking a mixture of 30 g (0.3 mole) of hexene-1-ol-5 (see above constants), obtained from reduction of allylacetone by metallic sodium in water-ether medium, and 6.3 g (0.08 mole) of pyridine was added dropwise. After addition of all of the mixture, the reaction mixture was distilled. From three experiments 116 g of crude product was obtained, which was washed with a weak alkaline solution, then with water, dried with anhydrous calcium chloride and then distilled through a fractionating column. As the result of distillation there were obtained: I) a fraction with b.p. 60-65° – 11 g; II) a fraction with b.p. 137-140° – 77 g; the above boiling residue was 20 g.

Upon repeated distillation, the 60-65° fraction boiled at 56-60°, and represented diallyl. Thus, along with replacement of the hydroxyl group by bromine, in the given instance there occurred a partial splitting out of HBr from the resulting bromide which, probably, again added to the diallyl forming a mixture of secondary and primary bromides (the residue boiling as above). For this reason, therefore, the 137-140° fraction was again redistilled, for the purpose of purification, through a good fractionating column, at which time 67 g of the substance of b.p. 137-138° at 708 mm was obtained. The yield was 45.6% of the theoretical.

$d_4^{20}$ 1.2005; $n_D^{20}$ 1.4636; $MR_D$ 37.44; calculated 37.21. 0.3020 g substance: 0.4887 g $CO_2$; 0.1848 g $H_2O$. 0.2544 g substance: 0.2934 g AgBr (Carius). Found %: C 44.13; H 6.80; Br 49.07. $C_6H_{11}Br$. Calculated %: C 44.17; H 6.75; Br 49.08.

Water-Alcohol-Alkali Reaction with the 150-151° b.p. Fraction. 32 g of the 150-151 b.p. fraction was added to 17 g of KOH solution in 100 ml of 95% alcohol, and the mixture was heated to boiling on a bath for 3 hours. At the same time potassium bromide separated. After termination of the heating, water was added, the upper layer of reaction product was separated, the water layer extracted with ether, the ether extractions combined with the main bulk of product was washed with water, dried with potash, and the ether distilled off, and the residue redistilled (almost completely in the 141-143° range). Since the boiling point of the substance was too low for the proposed alcohol, and corresponded more closely to the ethylhexenyl ether,

$CH_2=CH-CH_2-CH_2-CH_2-CH_2-O-C_2H_5$ [7], the liquid was boiled over metallic sodium for further purification, and was redistilled, at which time it boiled almost entirely at 139-139.5 (713 mm). The yield was 17.5 g (68.3%).

$d_4^{20}$ 0.7877; $n_D^{20}$ 1.4144; $MR_D$ 40.64; calculated 40.32. $d_4^{13}$ 0.7947; $n_D^{13}$ 1.4178.

0.1856 g substance: 0.5097 g $CO_2$; 0.2110 g $H_2O$. Found %: C 74.90; H 12.63. $C_8H_{16}O$. Calculated %: C 75.00; H 12.50.

Hexene-1-yl-6-acetate. 48 g of 6-bromohexene-1 was added to a hot solution of 50 g of anhydrous sodium acetate in 120 ml of glacial acetic acid. The mixture was heated to boiling on an oil bath for 18 hours, followed, after cooling, by dilution with water, separation of the upper layer, extraction of the liquid with ether, combination of the ether layer with the reaction product, washing with soda solution, then with water, dried with anhydrous calcium chloride, the ether distilled off, and the residue distilled through a fractionating column. Practically all of the substance boiled in the 166-170° range. The yield was 28.1 g, or 66% of the theoretical.

B.p. 169-170° at 704 mm; $d_4^{20}$ 0.8992; $n_D^{20}$ 1.4241; $MR_D$ 40.30; calculated 40.33.

0.2075 g substance: 0.5134 g $CO_2$; 0.1860 g $H_2O$. Found %: C 67.48; H 9.96. $C_8H_{14}O_2$. Calculated %: C 67.61; H 9.86.

Hexene-1-ol-6. 23.5 g of hexene-1-ol-6 acetic ester was heated to boiling on a bath with 15 g of KOH solution in 30 ml of alcohol for 3 hours, the mixture then diluted with water, extracted with ether, the ether extraction washed with water, dried with anhydrous potash, and the ether distilled off.

The residue, after removal of the ether, had a b.p. of 153-156°. The yield was 14.1 g (85.4%). B.p. 155.5-156° at 718 mm; $d_4^{20}$ 0.8453; $n_D^{20}$ 1.4364; $MR_D$ 30.95; calculated 30.97.

0.2832 g substance: 0.7465 g $CO_2$; 0.3087 g $H_2O$. Found %: C 71.89; H 12.11. $C_6H_{12}O$. Calculated %: C 72.00; H 12.00.

HBr Addition to 5-Bromohexene-1. Hydrogen bromide was passed into 104 g (0.63 mole) of 5-bromohexene-1 to an excess weight of 58 g (0.69 mole), with ice-salt cooling, and everything was then left overnight at room temperature. On the following day the reaction product was poured into water, washed twice with water, and then dried with anhydrous calcium chloride. Many crystals precipitated from the liquid upon standing at room temperature, the quantity of which was considerably increased upon standing in cooling mixture. The crystals removed from the liquid portion by suction filtration weighed 79 g (51% yield). After recrystallization from ether (by slow evaporation of the solvent) the substance melted at 38-39° and represented meso-2,5-dibromohexane [1]. The liquid portion of the reaction product was distilled in vacuo, at which time it almost completely boiled at 72-74° (4 mm). Yield was 57 g (36.7%). There remained in the distilling flask only a negligible residue (1.5 g) boiling as above, $d_4^{20}$ 1.5769; $n_D^{20}$ 1.5018; $MR_D$ 45.64; calculated 45.44 [97].

The yield of dibromides mixture was 136 g, or 87.8% of the theoretical.

## SUMMARY

1. 5-Bromohexene-1 and 6-bromohexene-1 were obtained by addition of hydrogen bromide to diallyl.

2. 5-Bromohexene-1 was likewise obtained from the reaction of $PBr_3$ with hexene-1-ol-5 in the presence of pyridine.

3. Hexene-1-yl-6-acetate and hexene-1-ol-6 were obtained from the reaction of sodium acetate in glacial acetic acid with 6-bromohexene-1 and with saponfication.

4. Upon reaction of HBr with 5-bromohexene-1 the addition proceeds according to Markownikoff's rule, and a mixture of stereoisomeric 2,5-dibromohexanes results.

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# SULFONATION OF UNSATURATED COMPOUNDS

## I. SULFONATION OF ACROLEIN AND OF CROTONIC ALDEHYDE

A. V. Dombrovsky

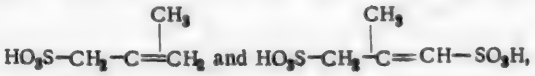
As far as is known, sulfonation of unsaturated aldehydes has not been achieved up to the present time, nor have their sulfo derivatives been obtained. The direct reaction of sulfonating agents on acrolein and on crotonic aldehyde leads to instant polymerization and resinification. A.P. Terentyev [1] has worked out for the first time a procedure for the introduction of the sulfo group into molecules of acidophobic compounds. A.P. Terentyev with his co-workers synthesized sulfo acids and their furane pyrrole and unsaturated hydrocarbon derivatives with one or two double bonds [2], using as the sulfonating agent complex-bound sulfuric anhydride with pyridine, so-called pyridine-sulfotrioxide.

The author attempted to use pyridine-sulfotrioxide for sulfonation of acrolein and of crotonic aldehyde. It was found that the heating of these aldehydes with pyridine-sulfotrioxide in sealed tubes at 80-100° led to extensive polymerization; but at room temperature the reaction proceeded so slowly that it was not possible to separate any considerable amounts of sulfonation products. Therefore, pyridine-sulfotrioxide was found to be an unsuitable sulfonating agent for these aldehydes.

Experimentation has indicated that a suitable and sufficiently convenient sulfonating agent for unsaturated aldehydes is found to be dioxane-sulfotrioxide – a complex compound between dioxane and sulfuric anhydride (I).

In 1906 A. E. Favorsky [3] investigated and obtained for the first time complex compounds of dioxane with bromine, iodine, sulfuric acid and others. Similarly in 1938 Suter and his co-workers [4] obtained dioxane-sulfotrioxide (I) and dioxane-disulfotrioxide (II) from the reaction of dioxane with a solution of sulfuric anhydride in dichlorethane:

As the authors indicated, the sulfonating action of complex (I) differs but little from the action of complex (II). Dioxane-sulfotrioxide proved to be a more potent sulfonating agent than pyridine-sulfotrioxide. It sulfonates many unsaturated compounds reasonably well at -10° and 0°, but is considerably less stable than pyridine-sulfotrioxide, and requires immediate use after its preparation. However, it can be preserved in a refrigerator for several days without noticeable decomposition. Isobutylene [5] and styrene [6] were sulfonated by the use of dioxane-sulfotrioxide. In the first instance there were isolated the sulfo acids:



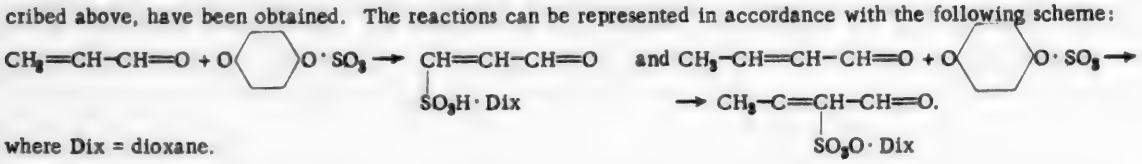
and styrene gave ω-styrene-sulfonic acid $C_6H_5-CH=CH-SO_3H$.

Dioxane-sulfotrioxide reacts vigorously in the cold (at 0°) with acrolein and with crotonic aldehyde. The reaction was carried out by gradual addition of an equivalent quantity of dioxane-sulfotrioxide to the unsaturated aldehyde in dioxane solution. The temperature of the reaction mixture was maintained at about 0° for the whole time. By controlling the extent of the sulfonation, monosulfonated acids of the corresponding aldehydes result. The reaction proceeds very rapidly. Completion of sulfonation is easily determined by cessation of the lachrymatory action and acrid odor of the aldehyde. If sulfonation is conducted at room temperature, and higher (about 50-60°), considerable darkening of the reaction mixture is observed due to the formation of resinous substances. Upon reverse addition of the components, i.e., upon addition of the aldehyde to the dioxane-sulfotrixoide solution, the monosulfo acids do not result, but rather products of higher sulfonation.

The initial products of sulfonation are the dioxane salts of the unsaturated aldehyde sulfo acids. These

salts dissolved in dichlorethane and hydrolyze instantly with water. Upon their treatment with a water suspension of barium carbonate, there occurs an exchange reaction in which the barium salts of the corresponding sulfoacids result. The potassium salts are easily obtained from the barium salts by interchange reaction with potassium sulfate. The potassium and barium salts of the acrolein sulfoacids and crotonic aldehyde are hygroscopic; they dissolve very readily in water. Their aqueous solutions are stable, and upon evaporation the salts crystallize out – stable indefinitely. The sulfoacid salts obtained possess unsaturated properties: their aqueous solutions decolorize potassium permanganate instantly, as well as bromine water. The carbonyl group in the aldehyde molecule was preserved in both cases after introduction of the sulfo group. Its presence was easily detected by the silver mirror test. The salts of the sulfo acids likewise reduce Fehling's solution to $Cu_2O$. Reaction for the carbonyl group was negative in all cases. This should apparently be explained as being due to the effect of a negative substituent, which is the sulfo group.

As a result of the procedures worked out for sulfonation of acrolein and of crotonic aldehyde, in yields of 96 and 75 % of theory, the monosulfoacids of the unsaturated aldehydes, whose salts possess the properties described above, have been obtained. The reactions can be represented in accordance with the following scheme:



where Dix = dioxane.

The position of the sulfo group was demonstrated by oxidizing the potassium salts of the sulfo acids in alkaline medium with potassium permanganate. Among the oxidation products were found carbonic acid, potassium sulfate and oxalic acid, the latter microscopically identified in the form of its calcium salt. Among the oxidation products of the crotonic sulfo acid, acetic acid was not there. As is known, a sulfo group situated at a carbon-carbon double bond is easily split off by oxidizing agents, converting into $SO_4^{=}$ ion [7].

The potassium salts of the sulfo acids are reduced in the presence of Raney nickel, one mole of hydrogen adding. After hydrogenation the salt solutions did not give reactions for the aldehyde group, but still decolorized $KMnO_4$ and bromine water as before. Consequently, the carbonyl group and not the double bond was reduced. Among the oxidation products for the reduced salts were found the same products as upon oxidation of the non-reduced salts. Such a type of hydrogenation is one more proof that the $SO_3H$- group is located at the double bond, which in the case given is shielded by the negative substituent.

The inactivity of a double bond which carries a negative substituent (-CHO, $-SO_3H$, or other) toward addition reactions is not an isolated case, but as a rule a double bond of such character is extremely difficult to reduce. But it should also be explained that many unsaturated carbonyl compounds do not add hydrogen, halogens, so forth, to the double bond, or that reactions proceed only with difficulty and with complications. For example, the the reduction of crotonic aldehyde with aluminum isopropoxide [8] proceeds without touching the double bond. With the divinylsulfoacid, obtained by direct sulfonation of divinyl, only one bond hydrogenates in the presence of nickel; the second to which is attached the $SO_3H$-group, remains untouched [9].

The free sulfoacids of the unsaturated aldehydes were not found to be stable to the same degree. The acrolein sulfoacid is stable in aqueous solution for an indefinite period. But when it is concentrated by evaporation on a water bath, rapid darkening of the liquid occurs, and the sulfo group is split off, with sulfuric acid formation. By cautious evaporation at room temperature in a vacuum dessicator, it is possible to isolate the free sulfoacid in the form of crystals, melting with decomposition at 98°. The crotonic sulfoacid is much less stable. When isolated in the free state, it decomposes in aqueous solution within a few hours, forming a resinous mass and sulfuric acid.

## EXPERIMENTAL

Dioxane-Sulfotrioxide Synthesis. 15 g (0.19 mole) of sulfuric anhydride was dissolved in 80 ml of dry dichlorethane, cooled in ice water. 16.5 ml (0.19 mole) of dioxane dried and distilled over KOH, was added in small portions, while stirring and cooling to 0°, to the $SO_3$ solution. The white, crystalline dioxane-sulfotrioxide precipitated immediately, which was still considerably dissolved in proportion to the amount of dichlorethane added.

Sulfonation of Acrolein. Freshly-prepared dioxane-sulfotrioxide solution was added in portions to a solution of 10.5 g (0.19 mole) of freshly-prepared acrolein (b.p. 52°) in 20 ml of dioxane, with stirring and cooling to 0°, whereupon rapid reaction occurred. In proportion to the dioxane-sulfotrioxide addition, the colorless solution

became colored, acquiring the color of tea by the end of the reaction. During sulfonation, negligible heat evolution was observed. After completing the addition of sulfonating agent, the reaction mixture was left at room temperature for 20-30 minutes. There appeared a small precipitate on the bottom of the flask, apparently the dioxane salt of the acrolein sulfoacid. Neither odor nor lachrymatory action was observed in the reaction mixture.

Acrolein Sulfoacid Salts. The initial sulfonation product was treated with a water suspension of 40 g of $BaCO_3$ in 200 ml of water to give a neutral reaction. After separation of $BaSO_4$, the light-yellow filtrate gave an abundant reaction for the barium ion and decolorized $KMnO_4$ instantly, as well as bromine water. The filtrate was evaporated on a water bath and 40 g of the barium salt was obtained.

0.1551 g substance: 0.0810 g $BaSO_4$. Found %: Ba 30.74. $C_3H_5O_4SBa_{1/2} \cdot H_2O$. Calculated %: Ba 30.96.

In order to remove the water of crystallization, the barium salt was boiled with benzene and then dried in a vacuum dessicator over sulfuric acid to a constant weight.

7.800 mg substance: 4.440 mg $BaSO_4$. Found %: Ba 33.50. $C_3H_5O_4SBa_{1/2}$. Calculated %: Ba 33.70.

The potassium salt was obtained by precipitating a hot solution of the barium salt with an equivalent quantity of potassium sulfate solution. The filtrate, containing the K-salt, likewise readily decolorized $KMnO_4$ solution and bromine water.

0.1662 g substance: 0.0816 g $K_2SO_4$. 6.737 mg substance: 5.210 mg $CO_2$; 1.002 mg $H_2O$. Found %: K 22.27; C 21.10; H 1.66. $C_3H_5O_4SK$. Calculated %: K 22.44; C 20.68; H 1.74.

A warmed solution of the acrolein sulfoacid potassium salt gave a silver mirror reaction (occasionally the silver precipitated in the form of a black precipitate) and reduced Fehling's solution.

6 g (0.034 moles) of the acrolein sulfoacid potassium salt in 60 ml of water was placed into a flask with 6 g of nickel prepared according to Raney. During 5 hours shaking at room temperature, 750 ml (about 0.034 mole) of hydrogen was consumed. Further absorption was practically nil. The reduced salt solution did not have a hydrogen sulfide odor, nor mercaptan odor, but decolorized $KMnO_4$ and bromine water as before. The silver mirror and the Fehling tests gave negative results.

3 g of the acrolein sulfoacid potassium salt in 50 ml of water was placed in a long-necked flask for oxidation, made slightly alkaline with potassium hydroxide and 11 g of finely powdered $KMnO_4$ added in small portions with continuous shaking. The oxidation proceeded with considerable heat and $CO_2$ evolution. To complete reaction, the flask contents were heated on a water bath for 2 hours (until the permanganate color disappeared). After removal of the manganese dioxide, the contents were evaporated to a small volume and treated with calcium nitrate solution. Acetic acid was added in slight excess to the white precipitate. Simultaneously a portion of the precipitate dissolved with $CO_2$ evolution (carbonates). The remaining precipitate was analyzed under the microscope. For this purpose, a drop of the suspension was placed on a slide, mixed with a drop of hydrochloric acid and left until crystals formed on the glass slide. At 8 to 15 magnifications under the microscope, a mixture of calcium sulfate and calcium oxalate crystals were distinctly observed. Upon oxidizing the reduced K-salt under similar conditions, calcium oxalate crystals were also found among the oxidation products under the microscope.

Sulfonation of Crotonic Aldehyde. 15.75 g (0.225 mole) of freshly-distilled crotonic aldehyde (b.p. 103-104°) was sulfonated according to the method described above with 37.8 g (0.225 mole) of dioxane-sulfotrioxide. After appropriate treatment with 50 g of barium carbonate, 36.5 g of the barium salt was isolated.

0.3648 g substance: 0.1968 g $BaSO_4$. Found %: Ba 31.71. $C_4H_5O_4SBa_{1/2}$. Calculated %: Ba 31.53.

The K-salt obtained likewise corresponded to the monosulfoacid:

0.3745 g substance: 0.1767 g $K_2SO_4$. 9.040 mg substance: 8.350 mg $CO_2$; 2.145 mg $H_2O$. Found %: K 21.17; C 25.20; H 2.65. $C_4H_5O_4SK$. Calculated %: K 20.77; C 25.52; H 2.68.

The crotonic sulfoacid potassium salt solution precipitated silver in the form of a mirror upon heating with an ammoniacal solution of $AgNO_3$; with Fehling's solution red $Cu_2O$ precipitated.

3 g (0.02 mole) of the crotonic sulfoacid in 30 ml of water was hydrogenated in a long-necked flask with 3 g of Raney nickel. During 4 hours, 357 ml (about 0.02 mole) of hydrogen was absorbed. The filtrate did not give a silver mirror test, and did not reduce Fehling's solution, but decolorized $KMnO_4$ and bromine water.

2 g of the K-salt was dissolved in 50 ml of water and 7 g of $KMnO_4$ was added in portions. Oxidation

proceeded with strong heat evolution in the reaction mixture. To complete the reaction, the mixture was heated on a water bath until the $KMnO_4$ color disappeared. Among the oxidation products, after appropriate treatment, there was found and identified calcium oxalate under the microscope by the crystal form. The K-salt reduced in the presence of nickel, and then oxidized, likewise gave oxalic acid.

## SUMMARY


1. Dioxane-sulfotrioxide is found to be a good sulfonating agent for acrolein and crotonic aldehyde.

2. Sulfocompounds of acrolein and of crotonic aldehyde were obtained and described for the first time.

3. The structures of the newly-obtained acrolein sulfo acid and crotonic aldehyde sulfo acid have been determined.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• See Consultants Bureau translation page 775.

# HYDROGEN ADDITION TO ACETYLENE DERIVATIVES

## THE CATALYTIC HYDROGENATION OF THE METHYL AND ETHYL ETHERS OF 2,7-DIMETHYLOCTADIYNE-3,5-DIOL-2,7*

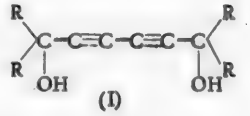
Yu. S. Zalkind** and Z. N. Kolyaskina

In the preceding works by one of the authors [1] on the addition of hydrogen to acetylene γ-glycols and their ethers, it was demonstrated that hydrogen addition to the above-mentioned compounds proceeds differently in the presence of platinum than in the presence of palladium.

In the presence of platinum black, the addition of 4 hydrogen atoms proceeds uniformly to the saturated compound. In the presence of palladium, however, there is noted a characteristic hydrogenation course, namely: 2 hydrogen atoms add rapidly to the molecule, and then the reaction rate decreases considerably. The selective action of the catalyst is evident—while acetylene glycol (ether) is present, ethylene does not enter into the reaction.

It was demonstrated [2], that the hydrogenation rate for the dimethyl and diethyl ethers is greater than for their corresponding glycol, however, with an increased weight in alkoxyl groups the hydrogenation rate decreases considerably.

It was of interest to investigate the properties of the diacetylene glycols and ethers and to compare their conformities to an established rule defined for the monoacetylene glycols and ethers. Derivatives with two triple bonds in the conjugated position are almost uninvestigated. Only isolated works [3,4] are known on the hydrogenation of glycols of type (I):



(I)

The ethers of the same series have not been investigated at all. The authors [3] who investigated these glycols indicate that the diacetylene glycol of 2,7-di-p-tolyloctadiyne-3,5-diol-2,7 conforms to an established pattern for the monoacetylene glycols when hydrogenated in the presence of palladium; Yu. S. Zalkind and L.F. Chelpanova [4] note the absence of such regularities for 2,7-dimethyloctadiyne-3,5-diol-2,7. Our research on the hydrogenation of the glycol of 2,7-dimethyloctadiyne-3,5-diol-2,7 and its ethers have likewise shown that selective hydrogenation, in the presence of palladium, of the diacetylene glycol of 2,7-dimethyloctadiyne -3,5-diol-2,7 and its ethers is absent.

Analysis of the hydrogenation products, after addition of 4 hydrogen atoms for one molecule of the hydrogenated substance to form 2,7-dimethyloctadiyne-3,5-diol-2,7 and its dimethyl and diethyl ethers, has shown that the hydrogenation products are a mixture containing 25-30% of the original diecetylene compound. The authors did not find the diethylene compounds.

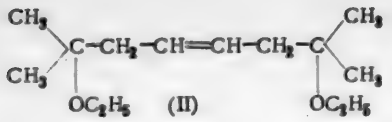
The 2,7-dimethyl-2,7-diethoxyoctadiyne-3,5 was investigated in greater detail.

The authors have carried out experiments on hydrogen addition, with intermissions after the absorption of 5 and 6 hydrogen atoms per molecule of hydrogenated substance, and to completion of the hydrogenation. A retardation of the reaction rate is observed after the addition of 6 hydrogen atoms; further addition proceeds very slowly and after addition of about 8 hydrogen atoms hydrogenation practically ceases.

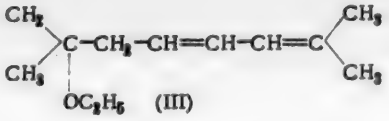
Examination of the hydrogenation products after the addition of 5 and 6 hydrogen atoms, and to completion of the hydrogenation, has demonstrated that in all instances there is present a mixture of products, saturated and unsaturated in composition. The authors were able to isolate a liquid with b.p. 113° at 11 mm (II), and a very small quantity of liquid with b.p. 96-99° at 15 mm (III) from the mixture after addition of 6 hydrogen atoms:

* For the synthesis of ethers of 2,7-dimethyloctadiine 3,5-diol-2,7 see the following article on page 2203.

** Deceased



(II)



(III)

It is possible that after the addition of 4 hydrogen atoms there forms an intermediate hydrogenation product – the acetylene ether, which in its turn after addition of 2 more hydrogen atoms gives the ethylene compound. It is quite probable that by precisely such a reaction course can be explained the retardation of the reaction rate after addition of 6 hydrogen atoms, characteristic for the acetylene bond, the more so that after addition of 6 hydrogen atoms the authors were able to isolate compound (II) in 55-60% yield. The structure of this compound (II) was proven by oxidation, wherein there resulted β-ethoxyisovaleric acid, acetic acid and acetone.

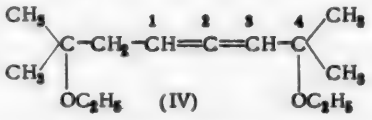
The authors had to determine further whether there was any of the original product in the mixture after addition of 6 hydrogen atoms. For this purpose hydrolysis was carried out, followed by reaction with metallic sodium, according to Bukhovets [5]. The reaction was negative. Consequently the mixture did not contain any of the original diacetylene ether, and by its disappearance might be explained the retardation of the hydrogen addition reaction.

Thus, these data indicate that the addition of hydrogen to diacetylene compounds proceeds in quite a complex manner. Hydrogenation was carried out in the presence of platinum black. Analysis of the hydrogenation products for 8 hydrogen atoms and for complete hydrogenation indicated that they likewise represent a mixture, saturated and unsaturated in composition.

After addition of 8 hydrogen atoms there was isolated from the mixture a liquid of b.p. 122-124° at 15 mm to the amount of 58-60% which was found to be similar in its structure to the full ether of the ethylene glycol (II) and to the aromatic mixture of b.p. 96-99° at 15 mm which was obtained in 12-15% yield and which was found to be similar to substance (III). The structure of this substance was proven by oxidation, wherein β-ethoxyisovaleric acid, oxalic acid, acetone and traces of acetic acid were obtained, which indicates that the substance is the ethyl ether of 2,7-dimethyl-octadiene-4,6-ol-2.

A. I. Lebedeva [6] obtained the corresponding diene alcohol by electrolytic hydrogenation of 2,7-dimethyl-octadiyne-3,5-diol-2,7, and she explains its formation by the dehydration of the ethylene glycol of 2,7-dimethyl-octane-4-diol-2,7.

It is possible that in our case there likewise occurs dealcoholation of the ether of this glycol (II), which leads to the formation of the ether of 2,7-dimethyl-octadiene-4,6-ol-2 (III). It is possible, however, that the formation of compounds with one ethoxyl group proceeds differently. If the hydrogen addition proceeds in such a manner that it forms an intermediate product of the allene type (IV):



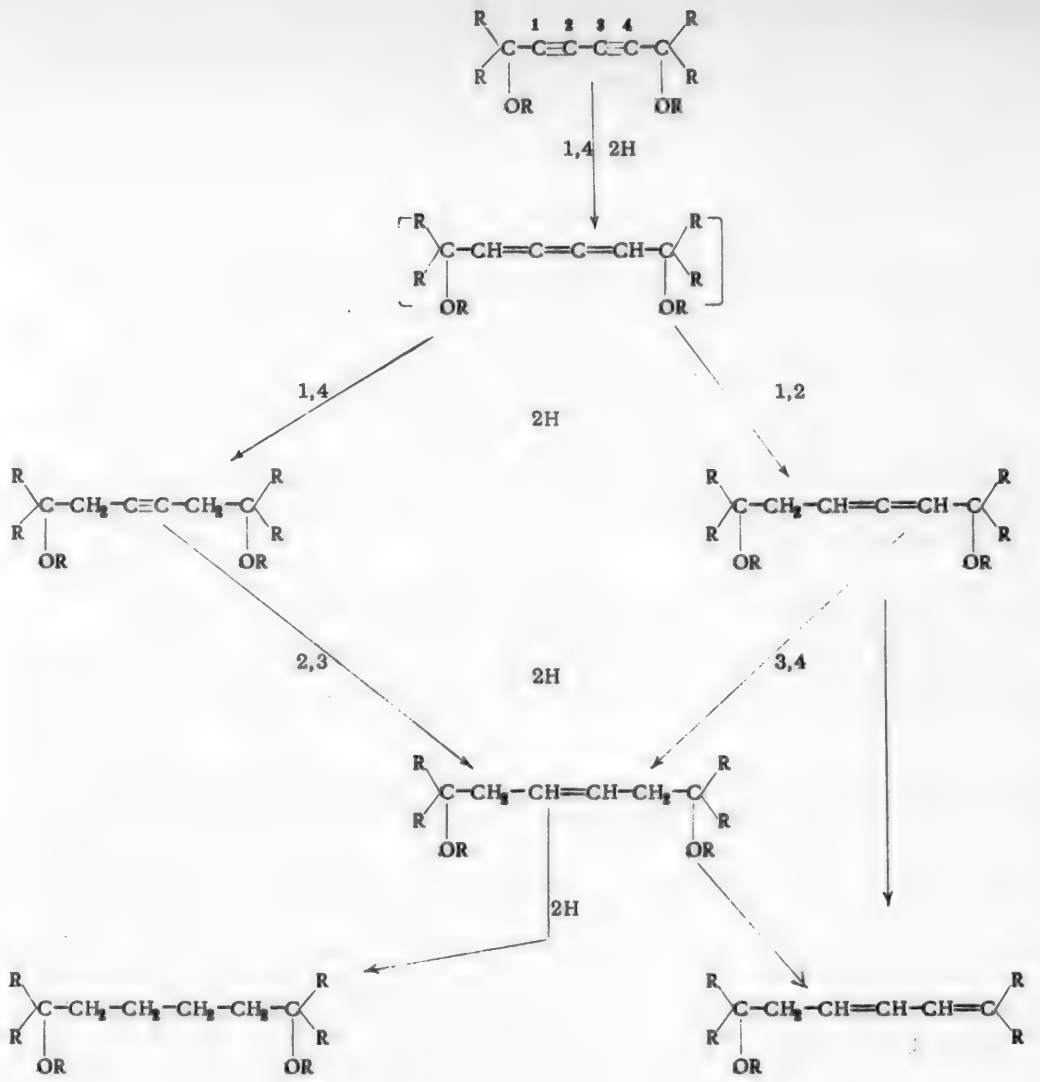
(IV)

then the presence of double bonds near to each other, and the oxygen atom of the ethoxyl group will produce an effect upon the fourth carbon atom which will promote the breaking away of the ethoxyl group. Possibility for the formation of the diethylene product is not excluded, although the authors failed to isolate it, regardless of the many experiments performed according to Diels-Alder.

Therefore, on the basis of the literature data [7,8,9,10] and the experimental data obtained by the authors, we consider it possible to assume the catalytic hydrogenation scheme to take the following form: (see next page)

Upon hydrogenation of 2,7-dimethyloctadiyne-3,5-diol-2,7 and its dimethyl and diethyl ethers in the presence of platinum, a certain analogy with the monoacetylene glycols and their ethers is observed during the course of hydrogenation.

As with the monoacetylene compounds, the addition of 8 hydrogen atoms proceeds with a smooth retardation in the rate of hydrogen addition, and the reaction does not terminate at this point, but rather proceeds further although very slowly to the addition of 10 hydrogen atoms, after which the hydrogenation practically ceases.




The analogy is also observed with variation in the character of hydrogenation in the presence of platinum and palladium, and this difference is evident not only in the hydrogenation course, but also in the number of hydrogen atoms added.

There is likewise observed in the hydrogenation rate of the glycol and the ethers an analogy with the monoacetylene compounds. Thus, the full methyl and ethyl ethers of the acetylene γ-glycols hydrogenate more rapidly than the glycol alone [2].

The diacetylene glycol ethers studied by the authors likewise add hydrogen more rapidly at the first moment than the glycol; but the difference between the hydrogenation courses of ethers and of glycol are insignificant. The quantity of catalyst affects only the hydrogenation rate.

## EXPERIMENTAL

### I. Catalytic Hydrogenation of 2,7-Dimethyloctadiyne-3,5-diol-2,7 and its Dimethyl and Diethyl Ethers.

The colloidal palladium was prepared on gum arabic. 0.0025 mole of the substance dissolved in 50 ml of water and 0.8 mg of palladium were taken for each experiment. The tests were carried out at 15°, and 757 mm on

one and the same day for complete comparability of the reaction course; $H_2$ 242 ml.

In Table 1 summary, t = time (in minutes) from start of the reaction; $\nu$ = the volume of hydrogen (in ml) absorbed from the start of reaction; $\%H_2$ = the same volume, given in percentage of theoretical volume, corresponding to the addition of 4 hydrogen molecules per molecule of substance.

In the Table 1 summary are cited data relating to 2,7-dimethyloctadiyne-3,5-diol-2,7 (A), to its dimethyl ether (B) and to the diethyl ether (C).

TABLE 1

| t | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $\nu$ | A | 13 | 25 | 37 | 53 | 67 | 79 | 92 | 104 | 116 | 128 |
| | B | 19 | 37 | 55 | 74 | 96 | 114 | 131 | 149 | 162 | 173.8 |
| | C | 14 | 26 | 40 | 54 | 68 | 83 | 97 | 110 | 124 | 137 |
| $\%4H_2$ | A | 5.41 | 10.33 | 15.28 | 21.90 | 27.68 | 32.64 | 38.01 | 42.97 | 47.98 | 50.00 |
| | B | 8.40 | 16.37 | 24.34 | 32.79 | 42.48 | 50.00 | 58.00 | 65.92 | 71.68 | 76.90 |
| | C | 5.85 | 10.87 | 16.73 | 22.55 | 28.45 | 34.73 | 41.00 | 46.02 | 51.88 | 57.32 |

Thus, at first hydrogen adds most rapidly to the dimethyl ether, and then to the diethyl ether, and it adds to glycol more slowly than to the ethers.

Further addition of hydrogen proceeds in such a way that the addition is quicker for the glycol. Apparently the stereochemical hindrances of the alkoxyl groups are evident here.

In the Table 2 summary are cited some data on hydrogenation runs for 2,7-dimethyloctadiyne-3,5-diol-2,7 (A), its dimethyl ether (B), and the diethyl ether (C). 1.6 mg of palladium, temperature 16°, pressure 750 mm; $H_2$ 244 ml.

TABLE 2

| t | | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\nu$ | A | 70 | 136 | 180 | 202 | 210 | 214 | 215 | – | 216 | – | 217 | 218.2 |
| | B | 173 | 178 | 180 | 181 | – | 182 | – | 183 | – | 184 | – | 186.6 |
| | C | 136 | 146 | 150 | – | 151 | – | 153 | – | 156 | – | 158 | 165.2 |
| $\%4H_2$ | A | 28 | 56 | 73 | 82 | 82.5 | – | – | – | – | – | – | 90 |
| | B | 70.90 | 73.00 | 73.47 | 73.81 | – | 74.18 | – | 75 | – | 75.41 | – | 76.40 |
| | C | 55.73 | 61.06 | 61.47 | – | 61.48 | – | 62.70 | – | 63.93 | – | 64.75 | 68.00 |

For the following experiment platinum black was used. Ethyl alcohol was the solvent.

In the Table 3 summary are cited data for the hydrogenation of 2,7-dimethyloctadiyne-3,5-diol-2,7 (A) and its diethyl ether (B) in the presence of 0.1 g of platinum at 16°; 753 mm; $H_2$ 246 ml (from calculation for two triple bonds).

Hydrogenation runs for the dimethyl ether of the same glycol also give analogous results. One of them is cited in Table 4.

0.2684 g of dimethyl ether, 0.1 g of platinum, 35 ml of alcohol, temperature 15°, pressure 753; $H_2$ 133 ml.

TABLE 3

| t | | 5 | 10 | 15 | 20 | 25 | 50 | 75 | 100 | 500 | 860 | 1200 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\nu$ | A | 11 | 20 | 25 | 30.2 | 35.8 | 61.2 | 84.4 | 103 | 195.8 | – | 245 |
| | B | 12 | 21 | 27 | 32.8 | 38.4 | 64 | 85.6 | 108.6 | 205 | 246 | |
| $\%4H_2$ | A | 4.5 | 8.1 | 10.1 | 11.9 | 14.5 | 24.8 | 34.3 | 41.8 | 79.1 | – | 99.6 |
| | B | 4.8 | 8.5 | 10.9 | 13.3 | 15.6 | 26.0 | 34.7 | 44 | 83.3 | 100 | |

Hydrogenation proceeds further, but very slowly.

TABLE 4

| t | 5 | 10 | 15 | 20 | 25 | 50 | 75 | 85 | 90 | 95 |
|---|---|---|---|---|---|---|---|---|---|---|
| p | 15.6 | 25.4 | 34 | 41.8 | 49 | 82 | 113.2 | 123.8 | 129 | 133 |
| %4H | 11.7 | 19.0 | 25.5 | 30.6 | 36.8 | 61.6 | 85.1 | 93 | 97 | 100 |

Hydrogenation also proceeds further.

II. Investigation of the Hydrogenation Products from 2,7-Dimethyl-2,7-diethoxyoctadiyne-3,5 Using Palladium.

1. After the addition of 4 hydrogen atoms, the palladium was precipiated, filtered off, the alcohol distilled off on a water bath, and the residue distilled in vacuo. A pleasant-smelling liquid was obtained which gave all the characteristic reactions for unsaturated compounds. The mixture was fractionally distilled at 8 mm; three fractions were obtained. The latter distilled within the narrow range of 113-115°, and contained 25% of the total mixture; in boiling point this liquid coincided with the original diacetylene ether, which was confirmed by hydrolysis: 0.82 g of the substance and 20 ml of 7% sulfuric acid and heating for 15 hours at a bath temperature of 70-75° with vigorous stirring. After appropriate treatment crystals were obtained, which gave a positive reaction for diacetylene glycol. Consequently this was the original diacetylene ester.

Other fractions were heated with maleic anhydride in benzene solution in sealed ampoules for 20 hours at 105-115°. Slight resinification was noted. Crystals did not precipitate upon cooling. The same was carried out on the hydrogenation product obtained after the addition of 5 hydrogen atoms. 2 g of maleic anhydride, 15 ml of benzene, 4 g of the substance. Heating was carried out at 105-115° for 16 hours. Upon cooling there was no sign of crystal precipitation.

2. After the addition of 6 hydrogen atoms the palladium was precipitated, filtered off, and the alcohol distilled off. 14 g of viscous liquid was left which gave all the characteristic reactions for unsaturated compounds.

A condensation reaction with maleic anhydride was carried out. 4 g of the substance, 2 g of maleic anhydride, 15 ml of dry benzene were heated for 10 hours at 110, 120 and 125°. Condensation products were not obtained.

To determine whether or not there was the original diacetylene ether among the addition products, 0.5 g of the liquid was hydrolyzed with 7% sulfuric acid solution. The hydrolysis product gave a negative result for the diacetylene glycol.

The remaining liquid obtained by hydrogenation was fractionally distilled to obtain three fractions, which were again fractionally distilled. After the fifth fractional distillation there was obtained: I) 85-95° (14 mm) – 0.1 g (strong aromatic odor); II) 101-106° – 1.2 g; III) 106-113° (13 mm) – 0.2 g; IV) 113° (11 mm) – 4.85 g.

Examination of the 113° b.p. fraction at 11 mm. The liquid, possessing properties characteristic for unsaturated compounds; was insoluble in water but soluble in many organic solvents: $d_{17}^{17}$ 0.8669; $d_4^{17}$ 0.8652; $n_D^{17}$ 1.4551. Found: $MR_D$ 71.11. $C_{14}H_{26}O_2$. Calculated: $MR_D$ 69.67.

0.1178 g substance: 0.3177 g $CO_2$; 0.1300 g $H_2O$. 0.1391 g substance: 0.3756 g $CO_2$; 0.1552 g $H_2O$. Found %: C 73.55, 73.63; H 12.26, 12.40. $C_{14}H_{26}O_2$. Calculated %: C 73.68; H 12.28. 0.1346 g substance; 15.38 g benzene: Δt 0.20°. 0.1162 g substance; 7.9147 g benzene: Δt 0.34°. Found: M 224.4, 221.9. $C_{14}H_{26}O_2$. Calculated: M 228. 0.1480 g substance: 0.2835 g AgI. Found %: $OC_2H_5$ 37.3. $C_{10}H_{18}(OC_2H_5)_2$. Calculated %: $OC_2H_5$ 39.5.

Oxidation of the 113° b.p. fraction at 11 mm. To determine the structure of the given substance, its oxidation with potassium permanganate was carried out, calculating on the basis of one double bond. 560 ml of 1% $KMnO_4$ solution was added with very rapid stirring to 30 g of water and 4 g of the substance. Oxidation continued for 8 hours.

After completion of reaction, the manganese dioxide was filtered off and washed with hot water. After cooling, the manganese dioxide and the filtrate were repeatedly extracted with ether. From the neutral products the acetone in the form of its 2,4-dinitrophenylhydrazone was identified, m.p. 122° (literature data = 126°) The remaining portion of neutral products was not examined due to the small amount involved.

The aqueous solution was steamed off and acidified with 10% $H_2SO_4$ solution. The acids were extracted three times with ether. The silver salts were obtained from the ammonium salt by fractional precipitation with silver nitrate.

Fraction I: 0.1155 g substance: 0.0484 g Ag. Found %: Ag 41.90. Fraction II: 0.0675 g substance: 0.0282 g Ag. Found %: Ag 41.77. $C_7H_{13}O_3Ag$. Calculated %: Ag 42.68.

The aqueous solution was extracted a second time with ether for 50 hours. The liquid obtained after distilling off the ether was heated with moist silver oxide. The silver salt obtained was analyzed:

0.0398 g substance: 0.0262 g Ag. Found %: Ag 65.83. $C_2H_3O_2Ag$. Calculated %: Ag 64.68.

Thus, β-ethoxyisovaleric acid and acetic acid were the results of the oxidation.

3. After addition of 7 hydrogen atoms in the presence of palladium, the hydrogenation practically stops, since more hydrogen adds extraordinarily slowly.

The liquid obtained was likewise a mixture and distilled in the range 110-118° at 10-13 mm. 4 fractions were obtained. All four fractions decolorized bromine water and potassium permanganate solution.

III. Investigation of the Hydrogenation Products of 2,7-Dimethyl-2,7-Diethoxy-octadiyne-3,5 with Platinum.

1. After the addition of 8 hydrogen atoms, the hydrogenation products from 2,7-dimethyl-2,7-diethoxyoctadiyne-3,5 were filtered off from the platinum and the alcohol was distilled off. 20 g of a viscous colorless liquid of pleasant aromatic odor remained. This liquid gave all of the reactions characteristic for unsaturated compounds. Several tests with maleic anhydride were set up, which gave negative results. The liquid was fractionally distilled under vacuo. After a fourth distillation at 15 mm, 5 fractions were obtained. I) 94-96° – several drops; II) 96-99° – 1 g – 11.75%; III) 103-107° – 1.6 g – 19%; IV) 114-118° – 0.9 g – 10.6%; V) 122-124° – 5 g – 58.65%.

All fractions decolorized bromine water and potassium permanganate solution. Elementary analysis data for the fractions of b.p. 103-107° and 114-118° indicated that these liquids are mixtures. Fraction II with b.p. 96-99°, and with b.p. 122-124° were examined in detail.

Investigation of the liquid with b.p. 96-99° at 15 mm. Colorless, very pleasant-smelling liquid, insoluble in water, readily soluble in many organic solvents:

$d_{18}^{18}$ 0.8098; $d_4^{18}$ 0.8096; $n_D^{18}$ 1.4509. Found: $MR_D$ 60.26. $C_{12}H_{22}O$. Calculated: $MR_D$ 58.53.

0.1031 g substance: 0.2941 g $CO_2$; 0.1198 g $H_2O$. 0.1333 g substance: 0.3815 g $CO_2$; 0.1545 g $H_2O$. Found %: C 77.78, 78.05; H 12.91, 12.87. $C_{12}H_{22}O$. Calculated %: C 79.12; H 12.10. 0.1175 g substance; 7.02 g benzene: Δt 0.46°. 0.1580 g substance; 7.62 g benzene: Δt 0.585°. Found: M 186, 181. $C_{12}H_{22}O$. Calculated: M 182. 0.1740 g substance: 0.2134 g AgI. 0.1068 g substance: 0.1292 g AgI. Found %: $OC_2H_5$ 23.5 23.6. $C_{10}H_{17}(OC_2H_5)$. Calculated %: $OC_2H_5$ 24.7.

Negative reaction with maleic anhydride.

Oxidation of the 96-99° b.p. fraction at 15 mm. 1 g of the substance was oxidized with 1% $KMnO_4$ solution. Oxidation was complete after 20 hours. After the oxidation, the manganese dioxide was filtered off and washed with hot water. Soda was added to the solution until the solution was alkaline, and the solution was heated for several minutes, the acetone distilled was characterized in the form of its 2,4-dinitrophenylhydrazone, with m.p. 120°. The acids were converted to the silver salts.

Fraction I 0.0638 g substance: 0.0270 g Ag. Found %: Ag 42.32. Fraction II 0.0678 g substance: 0.0289 g Ag. Found %: Ag 42.62. $C_7H_{13}O_3Ag$. Calculated %: Ag 42.68.

This corresponds to ethoxyisovaleric acid. From the aqueous solution remaining after the extraction of ethoxyisovaleric acid with ether, additional extraction was carried out in the extractor for 50 hours, at which time oxalic acid crystals were obtained, which were converted into the corresponding calcium salt.

On the basis of the data obtained, the structure, 2,7-dimethyl-7-ethoxy-octadiene-2,4 ester, should be assigned to the substance with b.p. 96-99° at 15 mm

Examination of the liquid with b.p. 122-124° at 15 mm. Colorless, oily liquid with very faint pleasant odor, insoluble in water but soluble in many organic solvents. Gave all of the reactions for unsaturated compounds:

$d_{22}^{22}$ 0.8643; $d_4^{22}$ 0.8633; $n_D^{22}$ 1.4556. Found: $MR_D$ 71.27. $C_{14}H_{26}O_2$. Calculated: $MR_D$ 69.77.

0.1154 g substance: 0.3122 g $CO_2$; 0.1296 g $H_2O$. 0.1423 g substance: 0.3839 g $CO_2$; 0.1546 g $H_2O$. Found %: C 73.78, 73.58; H 12.47, 12.07. $C_{14}H_{22}O_2$. Calculated %: C 73.68; H 12.28. 0.1671 g substance: 6.46 g benzene: $\Delta t$ 0.58°. 0.2292 g substance; 8.13 g benzene: $\Delta t$ 0.66°. Found: M 228, 219. $C_{14}H_{22}O_2$. Calculated: M 228. 0.1653 g substance: 0.3345 g AgI. 0.1550 g substance: 0.3102 AgI. Found %: $OC_2H_5$ 39.0, 38.5. $C_{10}H_{18}(OC_2H_5)_2$. Calculated %: $OC_2H_5$ 39.5.substance.

Oxidation of the fraction with b.p. 122-124° at 15 mm. 3.5 g of the substance was oxidized with 1% $KMnO_4$ solution. Upon vigorous mechanical stirring oxidation proceeded. 500 ml of the solution was added dropwise over a period of 4.5 hours. Further treatment was carried out by the usual procedures.

Ethoxyisovaleric acid, acetic acid and acetone resulted upon oxidation. Consequently the substance with b.p. 122-124° at 15 mm has the same structure as the 113° at 11 mm fraction, i.e., corresponds to 2,7-dimethyl-2,7-diethoxyoctene-4.

2. After absorption of 10 hydrogen atoms, hydrogen addition practically ceased. Upon examination of the hydrogenation products it was found that the liquid obtained distilled in the range 60-122° at 16-17 mm. 4 fractions were obtained. They all decolorized bromine water and potassium permanganate; all gave positive reactions for the ethoxyl group.

The fractions with b.p. 92-97° had $n_D^{18}$ 1.4494; this is close to the fraction 96-99° at 15 mm. The elementary analysis for carbon (78.75) is likewise close to the fraction 96-99° at 15 mm.

All of these data attest to the fact that in this case there is also obtained a mixture of substances in various stages of reduction.

## SUMMARY

1. A study of the catalytic hydrogenation of 2,7-dimethyloctadiyne-3,5-diol-2,7 and its dimethyl and diethyl ethers, has demonstrated that these compounds behave differently toward hydrogenation in the presence of platinum as against palladium.

2. It was found that in the presence of colloidal palladium there is no observable break in the hydrogenation rate of the ethers after the addition of 4 hydrogen atoms. The retardation of reaction rate is observed after addition of 6 H, and the reaction then proceeds with unusual slowness to 8 H. All of this points to the absence of selective hydrogenation of the triple bonds for the diacetylene glycols and their ethers.

3. It was demonstrated that the hydrogenation products after addition of 4, 5, and 6 hydrogen atoms per molecule of substance are found to be a mixture of varied composition.

4. Catalytic addition of hydrogen in the presence of platinum proceeds uniformly with slowing down at 8 hydrogen atoms; further addition proceeds with great slowness, and after 10 atoms the hydrogenation practically ceases. The hydrogenation products with platinum are likewise found to be a mixture.

5. As the result of catalytic hydrogenation there were obtained new compounds not described in the literature: 2,7-dimethyl-2,7-diethoxyoctene-4 and 2,7-dimethyl-7-ethoxyoctadiene-2,4.

6. On the basis of the literature and from the experimental data, a possible scheme for hydrogen addition to diacetylene ethers has been proposed.

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* See Consultants Bureau English Translation, p. 1281.

# THE SYNTHESIS OF ETHERS OF 2,7-DIMETHYLOCTADIYNE-3,5-DIOL-2,7

Yu. S. Zalkind* and Z. N. Kolyaskina

In a work by one of the authors [1] an assumption was made that ethers of tertiary acetylenic alcohols can condense like tertiary acetylenic alcohols [2] into the diacetylene ethers, in the presence of cuprous chloride.

3-Methyl-3-ethoxybutine-1 served as the object of investigation. The condensation was carried out in alcoholic solution in the presence of cuprous chloride, which was taken in the quantity of 15 g for 1 g of initial ether, and was dissolved beforehand in an aqueous solution of ammonium chloride. A few drops of concentrated sulfuric acid was added to the reaction mixture. The reaction was carried out with mechanical stirring and air was simultaneously passed through, and at the end—oxygen. After filtering off the condensation product, extraction was made with ether. A viscous oily liquid was obtained in a yield of 66%, with b.p. 91-96° at 6 mm, $d_{20}^{20}$ 0.9001, $n_D^{20}$ 1.4794, $MR_D$ 69.78. However, the liquid was not investigated in detail.

In this work our aim was to study in more detail the conditions for carrying out the condensation reaction, and likewise to investigate more thoroughly the compounds resulting after condensation, and to prove their structure.

3-Methyl-3-methoxybutine-1 and 3-methyl-3-ethoxybutine-1 served as starting compounds, which were obtained by splitting the monoethers of 2,5-dimethylhexine-3-diol-2,5.

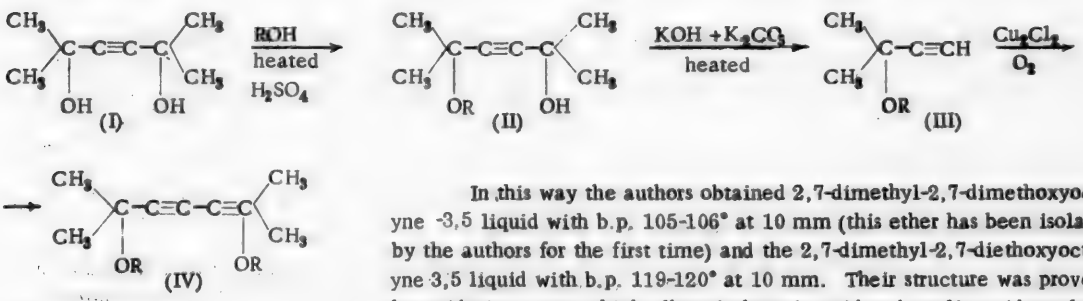
Conditions for carrying out the condensation to diacetylene ethers were changed somewhat. Hydrochloric acid was excluded from the reaction, and the cuprous chloride was taken in the ratio of 1 g per 1 gram of original substance, and isolation of the condensation products was carried out by treatment of the reaction mixture with 5-7% sulfuric acid with subsequent extraction with ether.

In a great number of experiments it was demonstrated that the condensation reaction can also proceed in the absence of solvent.

As the result of certain modifications in the condensation procedures, and with further treatment, we were able to achieve a condensation product yield of up to 85%.

2,5-Dimethylhexine-3-diol-2,5 (I) was synthesized by the method of Zh. I. Iotsich [3]. The monomethyl and monoethyl ethers of 2,5-dimethylhexine-3-diol-2,5 (II) were obtained by the method of Sh. Mamedov [4].

In the presence of a mixture of powdered potassium hydroxide and potash while heating [5], the obtained ethers were split into the acetone and the ethers of the acetylenic alcohol (III), which condensed into the diacetylenic ethers (IV).




(I) (II) (III) (IV)

R = $CH_3$ or $C_2H_5$.

In this way the authors obtained 2,7-dimethyl-2,7-dimethoxyoctadiyne -3,5 liquid with b.p. 105-106° at 10 mm (this ether has been isolated by the authors for the first time) and the 2,7-dimethyl-2,7-diethoxyoctadiyne 3,5 liquid with b.p. 119-120° at 10 mm. Their structure was proven by oxidation, upon which alkoxyisobutyric acid and oxalic acid resulted, and the glycol resulted upon hydrolysis. It appeared of interest to the authors to investigate the behavior of these ethers toward ethylmagnesium

* Deceased

bromide while heating. At the same time the hydrocarbon, 3,3,8,8-tetramethyldecadiine-4,6 was obtained.

## EXPERIMENTAL

I. 2,7-Dimethyl-2,7-diethoxyoctadiyne-3,5. Synthesis. 8 g of cuprous chloride and 16 g of ammonium chloride in 40 ml of distilled water were added to a flask equipped with two outlets into which were placed a dropping funnel and a gas outlet tube equipped with mechanical stirrer. To the solution obtained was added dropwise over a period of 1.5-2 hours, 7.2 g of the ethyl ether of dimethylacetylenecarbinol dissolved in 80 ml of ethanol. Oxygen was simultaneously passed through the agitated mixture (one may use air).

Reaction proceeded for 5-6 hours. After standing 10-12 hours, the solution was poured off from the precipitate, extracted several times with ether, at the same time a small amount of 5-7% sulfuric acid being added to remove the cupric chloride residue. The ether solution was then shaken 2-3 times with the sulfuric acid solution and was washed several times with water to remove sulfuric acid. The precipitate and the wash waters were again re-extracted 3-4 times with ether, and the ether extraction treated in the same manner; it was combined with the first and dried over sodium sulfate. After a second fractional distillation in vacuo at 10 mm, one fraction with b.p. 119-120° was obtained in the amount of 6 g.

This viscous colorless liquid (which turns slightly yellow upon standing) possessed a faint pleasant odor, was insoluble in water but soluble in benzene, alcohols, chloroform and other organic solvents, decolorized bromine water, potassium permanganate, and did not react with ethylmagnesium bromide under the usual conditions:

$d_4^{20}$ 0.8897; $d_4^{17}$ 0.8916; $n_D^{20}$ 1.4656; $n_D^{17}$ 1.4686. Found: $MR_D$ 69.04; $MR_D$ 69.19. $C_{14}H_{22}O_2$. Calculated: $MR_D$ 66.13 0.1295 g substance: 0.3600 g $CO_2$; 0.1141 g $H_2O$. 0.0837 g substance: 0.2319 g $CO_2$; 0.0737 g $H_2O$. Found %: C 75.81, 75.56; H 9.87, 9.79. $C_{14}H_{22}O_2$. Calculated %: C 75.67; H 9.90.

0.2946 g substance; 12.79 g benzene: $\Delta t$ 0.54°. 0.3456 g substance; 10.35 g benzene: $\Delta t$ 0.79°. Found: M 217.3, 216.9. $C_{14}H_{22}O_2$. Calculated: M 222.

0.1764 g substance: 0.3628 g AgI. 0.1866 g substance: 0.3861 g AgI. Found %: $OC_2H_5$ 39.7, 40.0. $C_{10}H_{12}(OC_2H_5)_2$. Calculated %: $OC_2H_5$ 40.5

For structure determination the substance was oxidized. To 6 g of the liquid under investigation there was gradually added 1 700 ml of a 1% potassium permanganate solution, calculated on the basis of complete rupture of two triple bonds. The oxidation proceeded at room temperature and was complete after 22 hours. The manganese dioxide was filtered off and washed with hot water. The filtrate and manganese dioxide were repeatedly treated with ether to isolate the neutral products. The aqueous solution, after acidification with sulfuric acid was extracted three times with ether (since there occurs hydrolysis of the alkoxyacids upon distillation with water vapor). The ether extraction was dried with sodium sulfate. The ether was not completely distilled. The ether solution was saturated with dry ammonia. The ammonium salt precipitate was dissolved in a few milliliters of water and was precipitated with silver nitrate. The silver salt precipitate was filtered off, washed, dried and analyzed.

Fraction I 0.0468 g substance: 0.0208 g Ag. Found %: Ag 44.44. Fraction II 0.1482 g substance: 0.0680 g Ag. Found %: Ag 45.78. $C_6H_{11}O_3Ag$. Calculated %: Ag 45.18.

Thus, the acid corresponded to ethoxyisobutyric acid. The aqueous solution was additionally extracted in an extractor. After distilling off the ether, crystals precipitated, which were pressed out on porcelain and dried. The crystals melted at 101.5°. A sample mixed with oxalic acid did not give a lowering of the melting point. By action of calcium chloride in the presence of ammonia the calcium salt resulted, which did not dissolve in acetic acid. Therefore, this was oxalic acid.

II. 2,7-Dimethyl-2,7-diethoxyoctadiyne-3,5 Hydrolysis. Hydrolysis was carried out for comparison with the monoacetylene ether and for demonstration of structure.

2 g of 2,7-dimethyl-2,7-diethoxyoctadiyne-3,5 and 50 ml of 7% sulfuric acid solution were heated on a water bath to 70-75° with vigorous agitation for 22 hours. The mixture was neutralized with the calculated quantity of soda and extracted with ether. The ether extraction was dried. After distillation of the ether, a viscous, straw-yellow colored liquid remained. The liquid redistilled at 12 mm with a b.p. of 123-125° and was found to be the original compound. An undistillable liquid residue was left in the flask which crystallized. After recrystallization from benzene, snow-white, fine needles were obtained, resembling superficially the glycol of 2,7-dimethyloctadiyne-3,5-diol-2,7. A sample mixed with the glycol did not give depression of the melting point.

In addition, a qualitative test for diacetylene glycol was carried out according to the method of Bukhovets [6], which gave a positive result. Diacetylene ethers do not give this reaction. Thus diacetylene ethers undergo hydrolysis with extreme difficulty under the above conditions indicated, whereas this reaction proceeds quite easily for the monoacetylene ethers.

III. Reaction of Ethylmagnesium Bromide with 2,7-Dimethyl-2,7-diethoxyoctadiyne-3,5. The organomagnesium compound was obtained beforehand from 4 g of magnesium and 19 g of ethyl bromide. To it was added dropwise 4 g of the diacetylene ether over a period of 2 hours while cooling (with ice water) and with mechanical stirring. The iced bath was then replaced by a water bath with a temperature of 36-40° and the heating was then continued for 10 hours.

After 8-10 hours the reaction mixture was decomposed with 30-35 ml of iced-water, the reaction flask being cooled. The reaction mixture was extracted with ether 5-7 times. The ether extract was dried with sodium sulfate. The ether was distilled off. A viscous, slightly colored liquid, with an odor different from that of the original ether, remained. After a second fractional distillation at 10 mm, two fractions were obtained. Fraction with b.p. 94-96° (1.9 g); decolorized bromine water, potassium permanganate, and gave a negative reaction for the ethoxyl group with hydrogen iodide.

$d_4^{19}$ 0.8308; $n_D^{19}$ 1.4692. Found $MR_D$ 63.46. $C_{14}H_{22}$. Calculated $MR_D$ 62.84. 0.0964 g substance: 0.3082 g $CO_2$; 0.0967 g $H_2O$. 0.0840 g substance: 0.2689 g $CO_2$; 0.0854 g $H_2O$. Found %: C 87.19, 87.30; H 11.14, 11.30. $C_{14}H_{22}$. Calculated %: C 88.43; H 11.57. 0.1584 g substance; 6.88 g benzene: $\Delta t$ 0.61°. 0.1541 g substance; 8.26 g benzene: $\Delta t$ 0.52°. Found: M 188.6, 181.8. $C_{14}H_{22}$. Calculated: M 190.

The substance obtained corresponds to the hydrocarbon, 3,3,8,8-tetramethyldecadiyne-4,6.

IV. 2,7-Dimethyl-2,7-dimethoxyoctadiyne-3,5 Synthesis. The synthesis was carried out under identical conditions. The starting substance was the methyl ether of 3-methyl-butine-1-ol-3:

B.p. 78-80°, $d_4^{17}$ 0.08000; $n_D^{17}$ 1.4020; $MR_D$ 29.81; M 96.

A viscous, colorless liquid was obtained yellowing with time, possessing a faint pleasant odor, soluble in benzene, alcohol, ether and insoluble in water, decolorizing bromine water and potassium permanganate:

B.p. 105-106° at 10 cm; $d_{20}^{20}$ 0.9146; $d_4^{20}$ 0.9122; $n_D^{20}$ 1.4677. Found: $MR_D$ 58.74. $C_{12}H_{18}O_2$. Calculated: $MR_D$ 56.89.

0.1304 g substance: 0.3542 g $CO_2$; 0.1038 g $H_2O$. 0.1446 g substance: 0.3927 g $CO_2$; 0.1179 g $H_2O$. Found %: C 74.07, 74.06; H 8.89, 9.05. $C_{12}H_{18}O_2$. Calculated %: C 74.22; H 9.27. 0.2967 g substance; 8.88 g benzene: $\Delta t$ 0.90°, 0.1071 g substance; 6.48 g benzene: $\Delta t$ 0.44°. Found: M 185.7, 187.9. $C_{12}H_{18}O_2$. Calculated: M 194. 0.1776 g substance: 0.4311 g AgI. 0.1523 g substance: 0.3543 g AgI. Found: % $OCH_3$ 32.6, 31.5. $C_{10}H_{12}(OCH_3)_2$. Calculated %: $OCH_3$ 32.0.

With this liquid analogous reactions were carried out, whereupon results similar to that of 2,7-dimethyl-2,7-diethoxyoctadiyne-3,5 were obtained.

## SUMMARY

1. The possibility of condensing ethers of acetylenic alcohols to the diacetylenic ethers of glycols was confirmed in the examples of 2,7-dimethyl-2,7-dimethoxyoctadiyne-3,5 and 2,7-dimethyl-2,7-diethoxyoctadiyne-3,5, which were characterized and their structure demonstrated. The first of these is not described in the literature.

2. It was demonstrated that the diacetylenic ethers obtained hydrolyze under the influence of 7% sulfuric acid, as do the monoacetylenic ethers of the γ-glycols, the former proceeding with greater difficulty.

3. It was demonstrated that by the action of ethylmagnesium bromide, the dimethyl and diethyl ethers of 2,7-dimethyloctadiyne-3,5-diol-2,7 exchange alkoxyl group for alkyl group, the result of which the hydrocarbon 3,3,8,8-tetramethyldecadiyne-4,6 is formed, which has not been described in the literature up to the present time.

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* See Consultants Bureau English translation page 757.

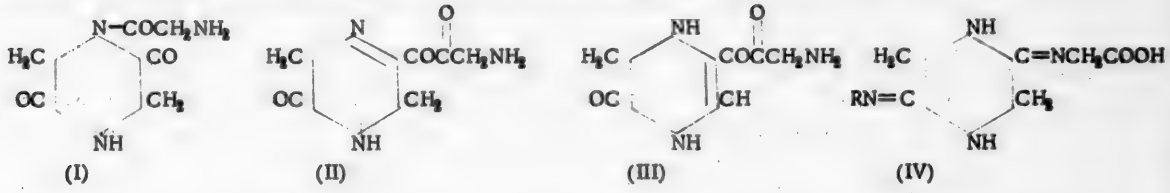
# THE STRUCTURE OF ALBUMIN

## X. SUBSTITUTED N-AMINOACYL DERIVATIVES OF DIKETOPIPERAZINE

L. N. Akimova and N. I. Gavrilov

After N.D. Zelinsky and V.S. Sadikov, and one of us (N. I. Gavrilov) proved definitely the origin of the cyclic forms of the bonds, the question arose as to the position of this structural unit in the albumin molecule. Different authors have answered this question differently. Thus, V.S. Sadikov and N.D. Zelinsky [1] attempted to visualize a bond between the separate diketopiperazines in the albumin molecule; they named such hypothetical combinations (similar to Fischer's peptides) "peptines" (polypeptines). A model structure, based upon diketopiperazines is known, proposed by Wrinch [2] and named "cyclol" by her.

In treating the question of the albumin molecular structure, many investigators have started from the three possible bond types of the diketopiperazines with amino acids and peptides (I, II, III):




(I) (II) (III) (IV)

The first bond (I) is that made possible by the nitrogen of the diketopiperazine. Its possibilities were extensively studied by Abderhalden and co-workers [3]. Up to the present time this type of bond, although it has been considered the most probable by many authors, has not been experimentally proven. The second (II) and the third (III) types of bonds, which are derivatives of the two enol forms of the diketopiperazines, are under discussion, but likewise have not been experimentally realized. Many authors—Karrer, Abderhalden, Bergmann, and and others—have synthesized only the acyl and the alkylhydroxyl derivatives of the enolized diketopiperazines, and up to the present no one has described the introduction of aminoacyl groups. Because the diketopiperazines are quite inert substances, and because albumin is extremely labile, all the investigations therefore have been based principally upon the enol forms of diketopiperazine. In turn, not one of these forms has been proved. If attempts for their experimental realization have been made, they have not progressed farther than the point of hypothetical construction.

Lately, the authors have also demonstrated the possibility of a fourth type of bond [4] for the diketopiperazines with aminoacyl groups (IV). The reality of such a bond was proved by the synthesis of a new group of compounds—the aminoacyldihydropyrazines, capable of transforming into amidines as the result of desmotropic regrouping, i.e., to form immediately derivatives of piperazine and not of dihydropyrazine:

But the above-enumerated bonds and the new structural grouping proposed by the authors can hardly be considered as the only contributions to the structure of such a complex system as albumin. On the contrary, the diversity of albumin bodies, their properties and varied functions compel one to assume a diversity of amino acid conjugation forms.

In the present work we have concerned ourselves both with the synthesis of the corresponding N-acyl derivatives of diketopiperazine, and with their various reactions, considering to be possible the existence of such a bond, along with the amidinic form.

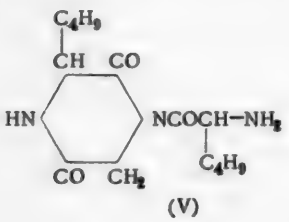
Many investigators have noted how difficult it is to hydrolyze dipeptides. In this respect diketopiperazine represents an even more inert substance than a dipeptide. It has been accepted that only the hydrogen on the nitrogen of diketopiperazine is very reactive. It is for this reason that the amide group has assumed the most dominant role in the search for the bond which connects diketopiperazines with amino acids.

In 1914 Maillard [5] obtained the first data on condensation between diketopiperazines and amino acids. By treating the amino acid mixture with a small quantity of glycerine, he isolated a mixture of substances which gave all of the typical reactions for albumin. It did not contain free amino acids, and upon this basis could be considered as consisting of diketopiperazine-amino acid derivatives. However, the individual substances were not isolated. Thus, Maillard first drew attention to the possibility of forming bonds between diketopiperazines and amino acids.

In 1925 Shibata upon heating albumin bodies in glycerine, obtained along with diketopiperazine, a substance which represented its derivative. It was not separated in its pure state, and therefore its structure was not determined.

Systematic work on the synthesis of diketopiperazines with side chains were carried out by Abderhalden and co-workers. However, Abderhalden went along a different line. Not aiming to find a bond between the individual diketopiperazines, he made an assumption concerning a bond between the latter and amino acids. According to Abderhalden, such a bond should be obtained by the aid of the diketopiperazine nitrogen and the carboxyl group of the amino acids or the peptides.

Methods for synthesizing such type compounds were many. Abderhalden attempting to decipher, with models, the work of Maillard, heated leucyl-glycyl-anhydride with leucine in glycerine, and obtained as the result, in his opinion, an anhydride with one amino acid at the nitrogen. The yield of substance obtained was 0.09 g, on the basis of 0.7 g of the anhydride and 0.54 g of leucine taken for reaction. The author does not mention qualitative reactions. According to analysis and molecular weight determination, the isolated compound coincided with leucyl-glycyl-leucyl anhydride. On the basis of analytical data only, the author made a decision on the structure of the compound, considering it to be the N-aminoacyl-derivative of leucyl-glycyl-anhydride (V):



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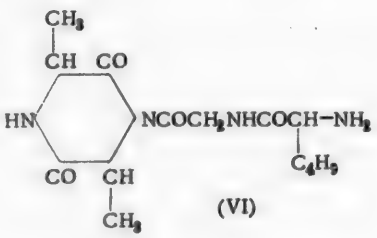


(VI)

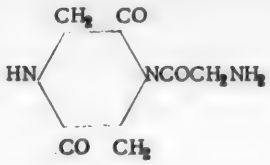
An analogous condensation was repeated with another amino acid – tyrosine. But in this case the heating of leucyl-glycyl-anhydride with tyrosine in glycerine did not lead to the individual compound. The substance obtained was characterized only by positive anhydride, ninhydrin and Millon reactions. The absence of analyses and yields make the author's assumption concerning the N-aminoacyl structure of this compound quite inconclusive.

In addition to heating in glycerine, condensation reactions were carried out in aniline. Upon boiling alanyl-alanyl-anhydride with the dipeptide, leucyl-glycine, in aniline, the investigators were able to isolate a substance representing a compound from these two components. From the analysis results (positive anhydride and ninhydrin reactions) the structure (VI) was assigned to it. The compound obtained did not give a biuret reaction.

A similar reaction was also carried out with serine anhydride and with the same dipeptide, leucyl-glycine, in aniline. At this time, the authors limited themselves to establishing only a ninhydrin reaction for the compound, pointing out at the same time the ability of the N-acyl bond to be split by pancreatin. The authors gave neither yield nor analysis nor properties other than theabsence of a biuret reaction. Consequently, the final structure of this compound was not determined.

The method of deriving the above compounds from the hydrochlorides of the tripeptide methyl esters gave considerably better results, in the opinion of Abderhalden. For this purpose the latter were left at room temperature for several hours, and sometime for several days in an ammoniacal solution of methanol, depending upon the amino acids contained in the tripeptide. The precipitated crystals were filtered off and analyzed.

In this way there was obtained from the diglycyl-glycine ester, the glycyl-glycyl-glycyl anhydride (VII):



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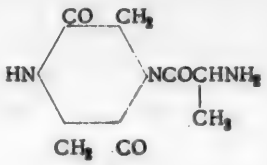
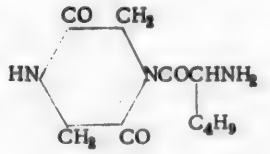


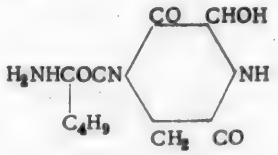
(VIII)

It was necessary to hold up on the analysis and purification of the substance. From the external appearance the precipitate from an ammoniacal methanol solution was found to be non-homogeneous, consisting of two substances. For their separation it was dialyzed, but the authors did not indicate by what they were guided in determining the completion of dialysis. The dialysate was then evaporated. The precipitate obtained gave a positive picrate reaction. The precipitate was found to be the diketopiperazine from the total nitrogen analysis. On the basis of the elementary analysis, the structure attributed to it was that of a diketopiperazine with a side chain. Inasmuch as the C, H and N content for the given compound is similar to that of diketopiperazine itself, then the essential proof for the structure attributed to the given compound would be the determination of amino nitrogen in it, which is just what the authors did not do.

By the same method alanyl-glycyl-glycyl-diketopiperazine (VIII) was obtained from the ester of alanyl-glycyl-glycine. Leucyl-glycyl-glycyl-anhydride (IX) was obtained from leucyl-glycyl-glycine. Leucyl-glycyl-seryl-anhydride (X) was obtained from leucyl-glycyl-serine:



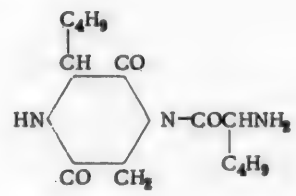
(IX)



(X)

Leucyl-glycyl-tyrosyl-anhydride was obtained from leucyl-glycyl-tyrosine. It is regretted that the authentic structures for these compounds were not worked out completely.

Apart from the reactions with tripeptide esters, investigations were carried out with the free peptides. Thus, upon heating the tripeptide of leucyl-glycyl-leucine with 15 times the quantity of glycerine at 180-190°, the authors observed anhydride formation without splitting off of the amino acid. The reaction product had the properties of substituted diketopiperazine (positive ninhydrin and anhydride reactions) and corresponded to the compound of structure (XI):



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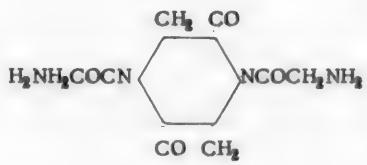


(XII)

However, they did not quote any other proof for such a structure. As has been demonstrated later, a similar cyclization of the methyl esters of the tripeptides – diglycylglycine, alanyl-glycyl-glycine and leucyl-glycyl-glycine, carried out according to Abderhalden, leads not to diketopiperazine amino acid derivatives, but to the free diketopiperazines and amino acids or to the cylcotripeptide.

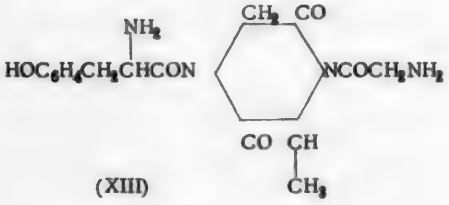
Quite interesting are the observations of Abderhalden and Schickel who obtained the dipeptide, alanyl-triptophane. They observed that, upon converting bromopropionyltryptophane into the corresponding dipeptide by means of ammonia, the anhydride is easily formed. A study of the properties of the latter points to its combination with the dipeptide. It is interesting that free amino groups were not found in the intermediate isovaleric compound, and that the anhydride failed to separate from the dipeptide. A spectrographic analysis of the substance has shown, in the course of an absorption curve, a great similarity with that from a mixture of the two components. On the basis of everything enumerated, the authors concluded that they were dealing with the N-aminoacyl compound of the anhydride.

Apart from the reaction reviewed, Abderhalden utilized the amination reaction of dichloracyl derivatives of diketopiperazine with ammonia to prepare diketopiperazines bonded to amino acids. To do this, the authors synthesized a series of N-haloidacyl derivatives of diktopiperazine and in particulary N,N'-dichloracetyl-diketopiperazine. By amination of the latter, Abderhalden and Clarmann intended to obtain the 1,4-diglycyl-2,5-diketopiperazine (XII). In the following year they synthesized dibromisocaryldiketopiperazine. Upon

treating the substance obtained with alcoholic ammonia, the authors obtained the free diketopiperazine, which case doubt upon the correctness of the formula which they attributed to the substance obtained by amination of dichloracetyldiketopiperazine.

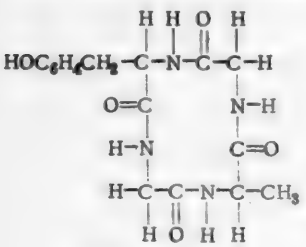
Thus, upon treating N-haloidacyl derivatives of diketopiperazine with ammonia, there occurred a simultaneous replacement of the halogen by the amino group and their decomposition to form the corresponding glycyl- or leucyl-amides and diketopiperazine.

Apart from attempts to obtain, synthetically, compounds of the N-aminoacyl type, Abderhalden and his coworkers were concerned with explaining the structures of substances obtained by partial hydrolysis of albumins, and they were considered by them to be combinations of diketopiperazines with amino acids. Upon hydrolysis of silk and of casein, Abderhalden isolated such anhydrides which definitely contained the diketopiperazine ring. Molecular weight determination showed that they consisted of three or four amino acids. Such a complex ring could only be formed at the expense of amino acid bonds (tyrosine on the one hand and glycocol on the other) with the nitrogen of diketopiperazine (glycyl-alanyl-anhydride). Quite interesting is the complete characterization of this substance, obtained by treatment of silk fibroin with 70% $H_2SO_4$, on the basis of which Abderhalden arrived at the structure (XIII):



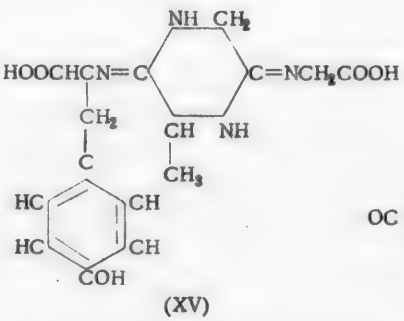
(XIII)

At first considering the isolated substance to be the tetrapeptide, tyrosyl-glycyl-alanyl-glycine, Abderhalden synthesized the analogous tetrapeptides and compared them with one another. The compounds isolated from silk did not give a positive ninhydrin reaction by the normal procedure, the reaction being positive only after prolonged boiling with ninhydrin. The presence of tyrosine was determined by a positive Millon test. The isolated substance was likewise characterized by a picric acid reaction and a weak biuret which appeared after standing for a while. The tetrapeptide obtained synthetically gave, on the other hand, a ninhydrin reaction but did not give a picric acid reaction. Abderhalden also studied the behavior of this substance with regard to 1 N alkali. The picric reaction disappeared if the isolated substance was heated with alkali or left standing for several hours at room temperature. At the same time a ninhydrin reaction appeared and an intensive biuret of red color. The latter attested to the breaking of the ring and the formation of a longer peptide chain. On the basis of these qualitative properties, only, Abderhalden arrived at the conclusion that the isolated substance was not identical with the tetrapeptide, but was instead the N,N'-diaminoacyl derivative of diketopiperazine. But, as follows from the formula attributed to it, this compound should have had free amine groups and a basic character. Abderhalden limited himself, however, only to the statement that this compound gave a qualitative ninhydrin reaction. He considered also another possible structure for this compound – that of the cyclotetrapeptide, from which clearly follows the neutral character of the compound and the absence of the amine group (XIV):

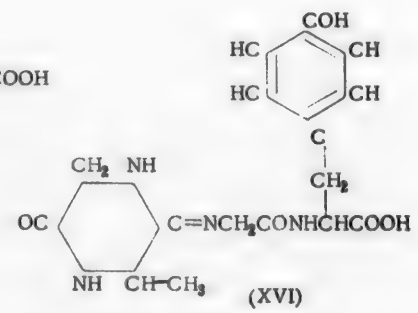


(XIV)

On the basis of the properties described by Abderhalden, one can hypothetically attribute to the compound the amidine structure (XV and (XVI) to this compound:



(XV)



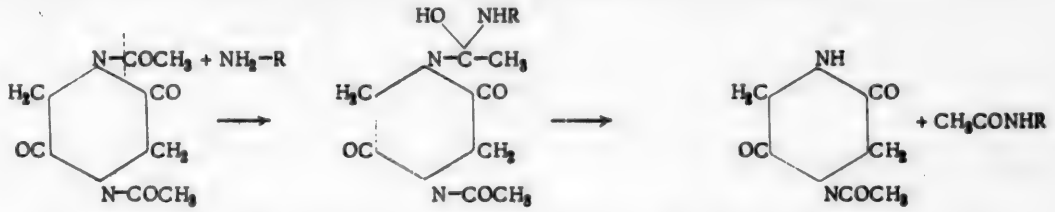
(XVI)

Thus, the multiple experiments carried out by Abderhalden with his co-workers on the synthesis of N-aminoacyl derivatives of diketopiperazines did not give satisfactory results. Numerous attempts to unite diketopiperazine with amino acids or with peptides by their direct interaction ended in failure.

In a majority of the cases characterization of the substances was limited only to analyses, and in some instances even they were not given, in which cases it can be definitely said that the authors were not dealing with the individual compound.

The above summary gives grounds for considering that Abderhalden's works on the N-aminoacyl type of bonding for the diketopiperazines is not sufficiently substantiated. Some interesting investigations bearing upon the possibility for the existence of the above-mentioned compounds in the free state were carried out by Bergmann [6] and Zehrwas. They obtained aceturic acid and the free diketopiperazine as the result of reaction of an alkaline solution of glycocoll with N,N'-diacetyldiketopiperazine.

This and the following observations led the authors to conclude that the bonding of diketopiperazine with amino acids by the nitrogen of the former should be unstable. Like diacetyldiketopiperazine, such compounds should be characterized by extreme lability toward ammonia and basic amino groups. From this point of view the negative experiments of Abderhalden and co-workers on the synthesis of N-diketopiperazine-amino acid derivatives can be explained by their ready cleavage and their difficulty of isolation:




Analogous reactions were explored in the works of Brunner [7] who utilized the acylamides for synthesis of amidines. The Brunner investigations gave an explanation to Bergmann's reacylation from the points of view stated in the present work.

Abderhalden's works found strong refutation in a series of articles, chiefly those of Bergmann and co-workers, and likewise in the investigations by one of us (N.I. Gavrilov) and Kh. N. Lerman [8], who demonstrated the impossibility of synthesizing N-aminoacyl-compounds by aminating N-haloidacyl diketopiperazines, and also by cyclizing tripeptide methyl esters. At the same time, the authors noted the formation of diketopiperazine in all cases.

No other attempts to unite diketopiperazines with amino acid or polypeptide groups through an amide bond are mentioned in the literature.

The above summary exhausts all of the information on synthesis of N-aminoacyl-derivatives of diketopiperazine.

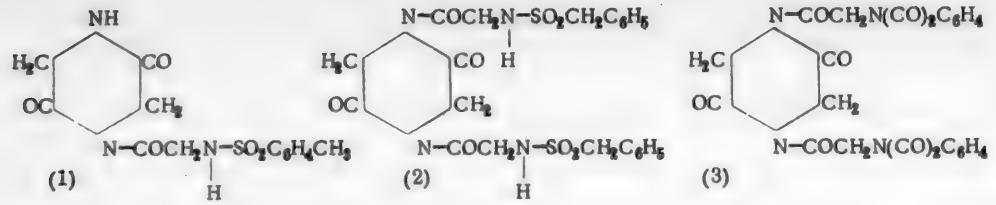
Since determination of the linkage between cyclic and the linear groupings is found to be essential for an explanation of the albumin structure, then the development of a synthetic method for making artificial models of such type compounds, and the study of their properties, is of utmost importance.

Having succeeded in demonstrating the amidine form of union and its likelihood in structural forms of albumin, we have drawn attention to the possibility of an N-aminoacyl combination of cyclopeptides with linear peptides. Having reviewed Abderhalden's failure to synthesize N-aminoacyl derivatives, in relation to the omission of the characteristic activity of the N-acyl compounds of diketopiperazines, the present authors nonetheless consider the synthesis of these compounds which may be present in the albumin structure, to be extremely important.

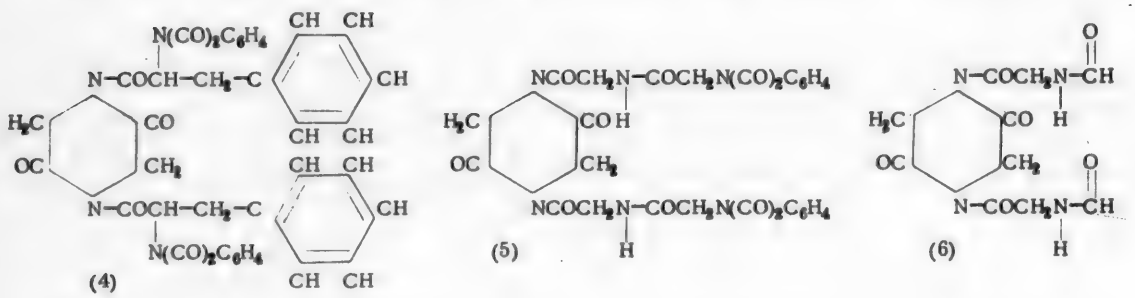
Direct aminoacylation of diketopiperazine was employed in approaching the problem of the synthesis of diketopiperazine with side chains. In the present work, the following N-aminoacylderivatives of diketopiperazine [1-6] were obtained: tolylsulfoglycyl-2,5-diketopiperazine [1], 1,4-dibenzylsulfoglycyl-2,5-diketopiperazine [2], 1,4-diphthalylglycyl-2,5-diketopiperazine [3], 1,4-diphthalylphenylalanyl-2,5-diketopiperazine [4], 1,4-diphthalylglycyl-glycyl-2,5-diketopiperazine [5] and N,N'-diformylglycyldiketopiperazine [6]: (see next page).

## EXPERIMENTAL

1. Tolylsulfoglycyl-2,5-diketopiperazine [1]. 3.7 grams of tolylsulfoglycylchloride obtained by Fisher [9], diluted with 50 ml of nitrobenzene, was heated with 0.85 g of diketopiperazine for 2 hours at 140°. Absolute ether was added to the hot filtered solution. The precipitate was filtered off, washed with alcohol and ether. The substance obtained had a melting point of 220°. It gave a positive anhydride reaction. According to analysis it was



(1) (2) (3)



(4) (5) (6)

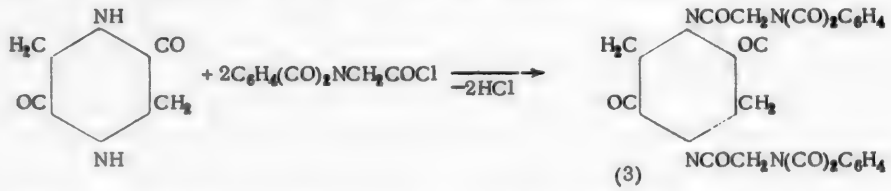
the monoacylated derivative of diketopiperazine.

6.760 mg substance: 0.793 ml $N_2$ (23°, 742 mm). 2.380 mg substance: 4.177 mg $CO_2$; 0.9548 mg $H_2O$. 3.156 mg substance: 5.536 mg $CO_2$; 1.289 mg $H_2O$. Found %: N 13.21; C 47.89, 47.87; H 4.49, 4.57. $C_{13}H_{15}O_5N_3S$. Calculated %: N 12.92; C 48.0; H 4.61.

2. 1,4-Dibenzylsulfoglycyl-2,5-diketopiperazine [2]. 1.3 g of benzylsulfoglycylchloride, obtained according to Johnson [10] was dissolved in 30 ml of nitrobenzene and heated with 0.3 g of diketopiperazine for 30 minutes at 140°. The hot solution filtered through a glass filter was precipitated by absolute ether. The precipitate which resulted upon standing was filtered and washed with alcohol. Recrystallized from nitrobenzene. Melting point of the substance obtained was 226° with decomposition. Positive anhydride reaction. According to analysis it was the diacylated derivative of diketopiperazine.

4.900 mg substance: 0.464 ml $N_2$ (23°, 737 mm). 3.005 mg substance: 5.455 mg $CO_2$; 1.170 mg $H_2O$. 3.105 mg substance: 5.625 mg $CO_2$; 1.250 mg $H_2O$. Found %: N 10.59; C 49.53, 49.45; H 4.36, 4.50. $C_{22}H_{24}O_8N_4S_2$. Calculated %: N 10.45; C 49.25; H 4.48.

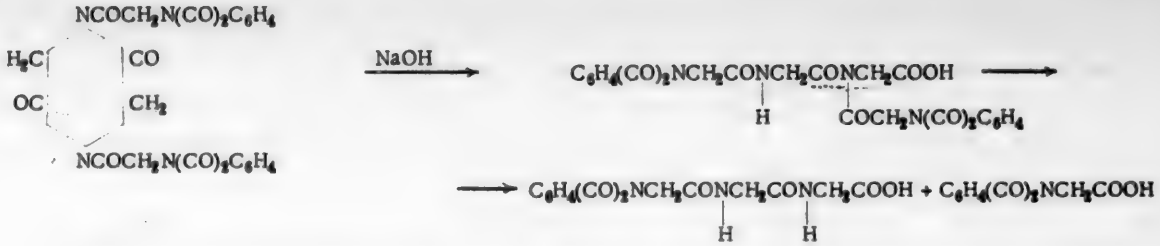
3. 1,4-Diphthalylglycyl-2,5-diketopiperazine [3]. Reaction proceeded according to the scheme:



(3)

1.9 g of phthalylglycylchloride obtained according to [11] was ground in a mortar with 0.48 g of diketopiperazine. The mixture was placed in a Gavrilov apparatus and 25 ml of dry xylene was added. Heating was carried out in Wood's alloy at the boiling point of the solvent (146°) for 5 hours. After cessation of reaction, the precipitate was filtered off and washed on a filter with benzene (to remove unreacted phthalylglycylchloride due to solubility in benzene). The precipitate examined under the microscope contained diketopiperazine. Therefore all of the precipitate was treated twice with boiling water in a flask. The last wash waters did not contain diketopiperazine (negative picrate reaction). After washing with hot water, the precipitate was washed on the filter with alcohol. The melting point of the substance recrystallized from nitrobenzene was 385° with decomposition. Yield 83%. Partially soluble in boiling xylene and methyl acetate, likewise in acetone. Picric and ninhydrin reactions were negative; biuret – of the tripeptide type (upon standing with alkali).

3.570 mg substance: 0.382 ml $N_2$ (25°, 721.5 mm). 3.535 mg substance: 0.367 ml $N_2$ (23°, 726 mm). 3.375 mg substance: 7.290 mg $CO_2$; 1.00 mg $H_2O$. 3.218 mg substance: 6.949 mg $CO_2$; 0.9232 mg $H_2O$. Found %: N 11.48: C 59.01; H 3.28.



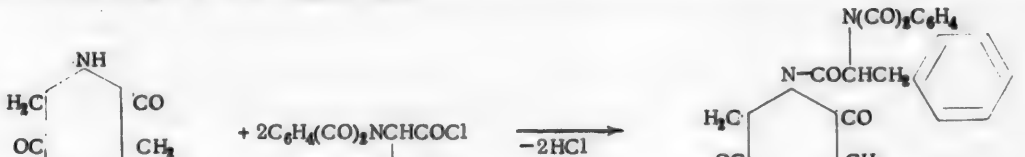
On the basis of spectrophotometry of the biuret reaction (maximum 590 mμ) the following decomposition of the substance in alkali can be assumed, which confirms the accepted structural formula above.

4. 1,4-Diphthalylphenylalanyl-2,5-diketopiperazine [4]. (a) Phthalyl-dl-phenyl-alanine synthesis [11], was carried out, with modification of the procedure used earlier. A mixture of 12.2 g of phthalic anhydride and 13.6 g of dl-phenylalanine was heated on an oil bath at 170-180° for 30 minutes. During this time solution took place accompanied by the formation of foam. After termination of reaction (transparent liquid) water was added to the mixture. Due to very poor solubility of phthalylphenylalanine in water, recrystallization was made from alcohol. For this purpose the fusion mixture was filtered from the water and dissolved in boiling alcohol. Upon concentration of the alcoholic filtrate a substance precipitated which was filtered off and washed with absolute alcohol. Because of the extremely good solubility of the substance in ether, and particularly in acetone, washing with these solvents is not recommended. M.p. 179°. According to the literature data [11], m.p. 177.5-179°.

(b) Phthalylphenylalanylchloride synthesis, was carried out in absolute benzene medium. A mixture of 2.36 g of phthalylphenylalanine and 1.67 g of $PCl_5$ was heated on a water bath at 60° with 10 times the weight of dry benzene. The mixture was shaken from time to time until a transparent solution resulted. About 30 minutes heating was needed for this. After cessation of reaction the solution was evaporated in vacuo, protected from the air moisture while heating. Upon concentration, the residue solidified immediately in the flask. Recrystallized from benzene + petroleum ether, m.p. 131°. Since the melting point of phthalylphenylalanylchloride (131°) obtained from benzene differed from the melting point of the chloranhydride of phthalylphenylalanine obtained from dioxane and described in the literature [11] (126°), the authors decided to analyze it.

6.010 mg substance: 0.235 ml $N_2$ (19°, 737 mm). Found %: N 4.42. $C_{17}H_{12}O_3NCl$. Calculated %: N 4.46.

(c) Synthesis of diphthalylphenylalanyl-2,5-diketopiperazine in dry xylene medium. The reaction proceeds according to the following scheme:

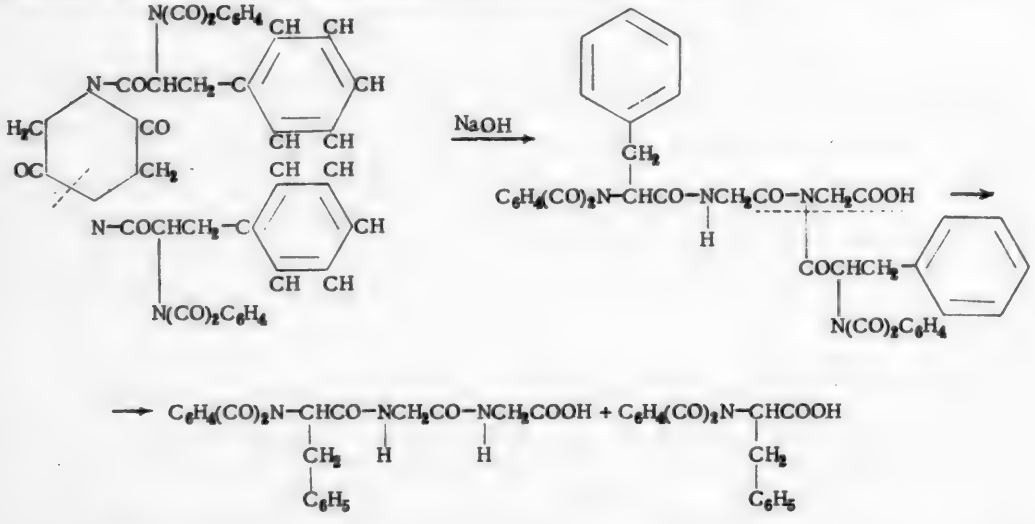


0.55 g of diketopiperazine was ground in a mortar with 3.15 g of phthalylphenylalanylchloride. The mixture was placed in a flask with a reflux condenser and 40 ml of dry xylene was added. Heating was carried out in a Wood's alloy bath for 6 hours at the boiling point (160° in the alloy). After 30 minutes everything was dissolved. Reaction continued for another 5 hours and 30 minutes. Upon termination the solution was cooled. The resulting precipitate was filtered off and washed with acetone. From the acetone filtrate a substance was isolated by precipitation with absolute ether, composed of well-defined rods, as seen under the microscope. M.p. 210°, not soluble in anything. Anhydride reaction was negative, biuret – tripeptidic upon standing with alkali. Maximum absorption at 590 mμ. Total nitrogen 7.81%.

A precipitate formed from the basic xylene filtrate upon standing for 3 days, which was filtered off and washed on the filter with acetone and absolute ether. The substance isolated had the same properties as the above-mentioned. Total nitrogen 8.41%. M.p. 244°. Total yield 75%.

2.795 mg substance: 0.206 ml $N_2$ (18°, 740.5 mm). 2.965 mg substance: 7.435 mg $CO_2$; 1.150 mg $H_2O$. 2.970 mg substance: 7.460 mg $CO_2$; 1.170 mg $H_2O$. Found %: N 8.41; C 68.38, 68.48; H 4.33, 4.31. $C_{38}H_{28}O_8N_4$. Calculated %: N 8.38; C 68.26; H 4.19.

On the basis of spectrophotometric data for the biuret complex of this compound, can be judged the mechanism of its decomposition under the influence of alkali. This decomposition is similar to the decomposition of the earlier-described 1,4-diphthalylglycyl-2,5-diketopiperazine.



(d) Synthesis of 1,4-diphthalylphenylalanyl-2,5-diketopiperazine in nitrobenzene. 0.55 g of finely-powdered diketopiperazine was mixed with 3.15 g of phthalylphenylalanylchloride. The mixture was placed in a three-necked flask equipped with a reflux condenser and stirrer. 40 ml of nitrobenzene was added to the mixture and the mixture was heated in Wood's alloy at 160°; within thirty minutes everything was dissolved. Upon heating for an additional hour, the solution began to resinify, which forced termination of the reaction. Absolute ether was added to the cooled nitrobenzene solution. The substance precipitated at the same time was filtered off and washed with absolute ether. The substance did not give an anhydride reaction. Biuret reaction – tripeptide, upon standing with alkali. M.p. 244°. Yield 45%. Upon standing three days, a precipitate formed in the nitrobenzene filtrate, which was filtered off and washed on the filter with acetone. M.p. 245°. Properties: insoluble in boiling water, insoluble in organic solvents. Biuret reaction – tripeptidic. Anhydride reaction negative.

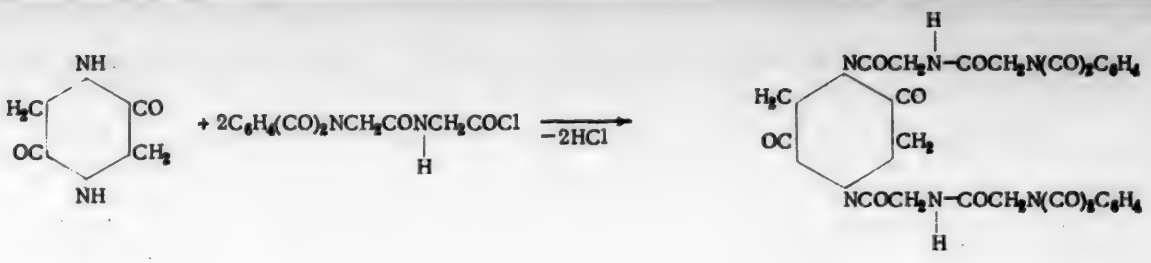
5. 1,4-Diphthalylglycylglycyl-2,5-diketopiperazine [5]. (a) Phthalylglycylglycine synthesis was carried out by the method indicated for phthalylglycine [12], i.e., by melting phthalic anhydride with glycylglycine. Melting point of the phthalylglycylglycine recrystallized from water was 231°.

(b) Phthalylglycylglycylchloride synthesis. 3.2 g of phthalylglycylglycine ground beforehand in a mortar was mixed with 3.2 g (2.54 g for theory) of $PCl_5$ in a Gavrilov apparatus. 100 ml of dry benzene was then added. The mixture was heated on a water bath for 2 hours at 80°. The solution, while still hot, was filtered off from the precipitate (into a second chlorinator). The transparent filtrate was concentrated in vacuo to a small volume by heating. The precipitate formed was filtered off and washed with absolute ether. M.p. 128° with decomposition.

6.900 mg substance: 0.612 ml $N_2$ (25°, 749 mm). Found %: N 10.02. $C_{12}H_9O_4N_2Cl$. Calculated %: N 9.98.

(c) 1,4-Diphthalylglycylglycyl-2,5-diketopiperazine synthesis.

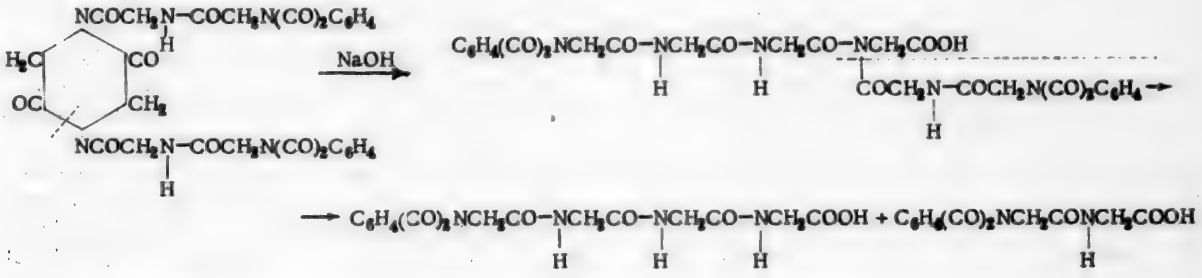
1 g of phthalylglycylglycylchloride was dissolved in 10 ml of nitrobenzene (very readily soluble). The solu-



tion was placed in a three-necked flask equipped with mechanical stirrer, wherein 0.2 g of finely-powdered diketopiperazine had been previously powdered. The mixture was heated in Wood's alloy at 140° for one-hour. Heating was accompanied by coloration. After completion of reaction the solution was cooled and filtered from the precipitate, which was found to be diketopiperazine. The filtrate was precipitated with absolute ether. The resulting precipitate was filtered off and washed on the filter with methyl acetate. The resulting precipitate was absolutely insoluble in boiling water as well as in organic solvents. It gave a strong anhydride reaction upon gentle heating. The biuret reaction was of the tetrapeptide type (upon standing with alkali). M.p. above 340°.

3.490 mg substance: 0 435 ml $N_2$ (22°, 743 mm). 5.591 mg substance: 0.530 ml $N_2$ (24°, 745 mm). 2.415 mg substance: 5.945 mg $CO_2$; 0.7724 mg $H_2O$. 3.170 mg substance: 6.275 mg $CO_2$; 0.9831 mg $H_2O$. Found %: N 14.09, 13.98; C 55.83, 55.98; H 3.58, 3.47. $C_{22}H_{22}O_{10}N_6$. Calculated %: N 13.95; C 55.81; H 3.65.

On the basis of spectrophotometric data for the biuret complex, an idea about the manner of disintegration of this substance under the influence of alkali can be drawn up. This disintegration was confirmed by the presence of two maxima at 535 mμ and at 620 mμ, and is analogous to the decomposition of 1,4-diphthalylglycyl-2,5-diketopiperazine, as can be presented by the following scheme:



6. N,N'-Diformylglycyldiketopiperazine synthesis [6]. 0.5 g of finely-powdered formylglycine [13] was introduced into the chlorinator and 3.12 ml of freshly-distilled acetyl chloride and 1.06 g of finely-powdered and freshly-prepared $PCl_5$ was added. All of the formylglycine dissolved upon shaking and cooling. The solution was evaporated in vacuo to dryness. The dry residue in the chlorinator was treated three times with dry petroleum ether to remove phosphorous chloroxide. 30 ml of dry benzene was added to the precipitate in the chlorinator plus 0.2 g of finely-ground diketopiperazine. Upon heating on a water bath at 60°, vigorous evolution of hydrogen chloride was observed in the first 15-20 minutes. Heating was continued at 70°. Evolution of hydrogen chloride proceeded at a slower rate. Heating was continued for 5 hours. After completion of reaction, the precipitate was filtered off and washed on the filter, first with dry acetone and then with ether. The substance obtained was soluble in formic acid, slightly soluble in alcohols, ethyl and methyl acetates, and in water. It gave a vigorous anhydride reaction in the cold. Upon heating in a capillary, it decomposed at about 200° with intense darkening.

0.0702 g substance: 8.86 ml 0.1 N NaOH (corresponding to 8.86 ml 0.1 N $H_2SO_4$). Found %: N 20.20. $C_{10}H_{12}O_6N_4$. Calculated %: N 19.7.

Due to the very poor yield of substance in the second stage of the synthesis, the preparation of formylglycylchloride was abandoned

7. N,N'-Dicarbobenzoxyalanyldiketopiperazine synthesis. (a) Condensation reaction in xylene. 1st experiment: 0.25 g of finely-ground diketopiperazine was mixed with 1.3 g of carbobenzoxyalanylchloride in 10 ml of dry xylene. It was heated in Wood's alloy for 10 minutes at 120°. HCl was evolved. After cessation of reaction, the precipitate was filtered off and washed with absolute ether. The substance obtained

did not contain chlorine, and did not give a positive ninhydrin reaction. The anhydride reaction was strong in the cold. The crystals precipitated from water were different from diketopiperazine.

2nd experiment: 3.3 g of carbobenzoxyalanine and 3.5 g of $PCl_5$ were taken for reaction. Reaction was carried out in absolute ether. The ether was removed in vacuo, and the residue in the form of an oil was extracted three times with absolute petroleum ether and then dissolved in absolute xylene. A xylene solution of carbobenzoxyalanylchloride was mixed with 0.42 g (50%) of powdered diketopiperazine. The mixture was heated on Wood's alloy to the cessation of HCl evolution; at the same time everything resinified in the first 15 minutes. The precipitate was then filtered off and treated on the filter with methanol and water in the cold. A portion dissolved. The undissolved portion represented diketopiperazine. A drop of the aqueous filtrate under the microscope represented a mixture of the diketopiperazine and of a new substance (small rhomboids).

It was observed that upon condensing carbobenzoxyalanylchloride with diketopiperazine in xylene there occurred strong resinification, even upon heating on the water bath. It was therefore necessary to substitute another solvent for xylene. Reactions were carried out in absolute benzene and in ether media. The most interesting results were obtained upon conducting the reaction in absolute ether.

(b) Condensation reaction in ether. 3rd experiment. 2.2 g of carbobenzoxyalanine and 2.1 g of $PCl_5$ were taken for reaction. The reaction was carried out in absolute ether medium. After completion, the ether was distilled off in vacuo and the oil, treated three times with petroleum ether, was dissolved in absolute ether and used for the condensation reaction with diketopiperazine.

Upon heating carbobenzoxyalanylchloride with 0.25 g of diketopiperazine in absolute ether, HCl did not evolve in the first 10 minutes. After a half hour of boiling, the precipitate was examined under the microscope. From water it had the form of diketopiperazine. The precipitate did not change externally during the time of reaction in ether. Then, having removed the ether from the reaction flask by simple heating with the condenser disconnected, xylene was added to the flask and heated. Upon heating, HCl evolution was observed and the precipitate yellowed. After completion of reaction (cessation of HCl evolution) the precipitate was filtered off. Examination under the microscope showed that, along with the dendritic diketopiperazine were other crystals. The precipitate was treated with methanol in the cold It was filtered off. The methyl alcoholic filtrate was concentrated. The precipitate formed was filtered off. The precipitate gave an anhydride reaction in the cold. Soluble in glacial acetic acid. Recrystallized in the form of small rhomboids. However, diketopiperazine was likewise soluble in acetic acid. Therefore it was impossible to separate the precipitate which was of interest to us from diketopiperazine by recrystallization from glacial acetic acid. An attempt to recrystallize the substance from nitrobenzene was unsuccessful. Upon heating in the latter there occurred considerable resinification. Due to the enumerated difficulties (choice of solvent for recrystallization) the authors limited themselves to double treatment of the precipitate with absolute methanol. The precipitate obtained by concentration of the methanol filtrates was analyzed.

7.195 mg substance: 0 706 ml $N_2$ (20°, 738 mm). 6.320 mg substance: 0.501 ml $N_2$ (25°, 736 mm). Found %: N 11.85, 11.81. $C_{16}H_{28}O_8N_4$. Calculated %: N 10.69.

According to the nitrogen content, the substance was contaminated with 10% of diketopiperazine. The difficulty in separating the resulting substance from diketopiperazine prevented the use of this method for derivation of N-aminoacyldiketopiperazine.

## SUMMARY

Starting from the above-quoted literature review it follows that the problem of N-acylated diketopiperazines appears to be a most interesting and important problem, both in synthesis and in albumin transformation.

The impossibility of the N-aminoacyldiketopiperazine synthesis route chosen by Abderhalden was demonstrated by the work of Bergmann and the authors. Therefore, up to our time no one has succeeded in obtaining N-aminoacyl derivatives of diketopiperazines.

Upon reviewing the unsuccessful attempts of Abderhalden to derive such type compounds, conditioned chiefly by the great reactivity of the N-acyl derivatives of diketopiperazine, the authors believe that their synthesis is extremely important. Starting from the ease of acylation of diketopiperazines by chloranhydrides of acids, the authors have obtained the following N-aminoacyl derivatives of diketopiperazine: (1,4) N,N'-dibenzylsulfo-, (1,4) N,N'-ditolylsulfo- (1,4) N,N'-diphthalylsulfo (1,4) N,N'-diformylglycyl- and (1,4) N,N'-

diphthalylglycylglycyl-2,5-diketopiperazines. Upon investigating further the transformations of these compounds, we have found that their lability is generally characteristic for all N-acyl derivatives of diketopiperazine.

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# THE STRUCTURE OF ALBUMIN

## XI. SOME REACTIONS OF DIACYLDIKETOPIPERAZINES

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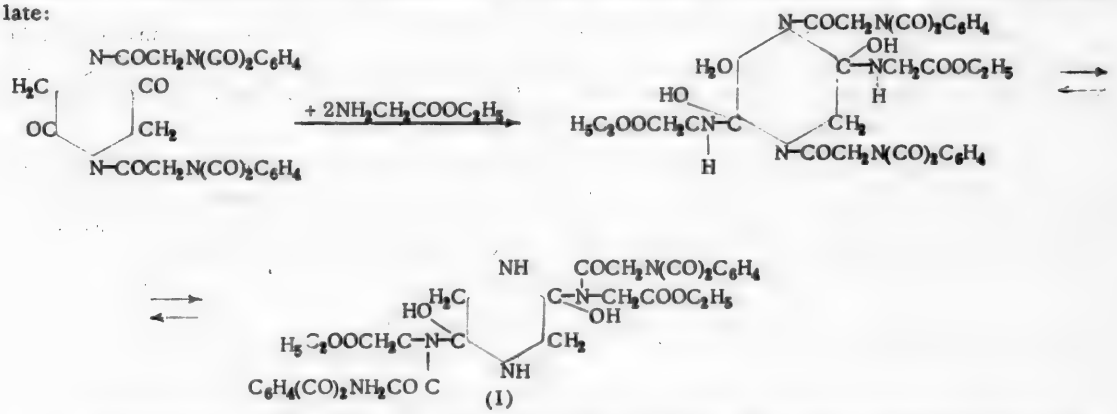
In the preceding article [1], the authors have demonstrated the ease of acylation of diketopiperazine by amino acid chloranhydrides with protected amino groups. There resulted nitrogen substituted diketopiperazines (N,N'-diaminoacyldiketopiperazines). The synthesis of phthalyl derivatives of amino acids were of most interest. Their chloranhydrides were especially easy to condense with diketopiperazine to form N,N'-diphthalylamino-acyldiketopiperazines.

Upon reacting phthalylglycylchloride with diketopiperazine, an almost quantitative yield of 1,4-diphthal-ylglycyl-2,5-diketopiperazine was formed. This complex N-aminoacyl-derivative of diketopiperazine behaves in exactly the same manner as the other(simpler) N-acyl derivatives of diketopiperazine, as has been demonstrated in the present work.

Using the addition reaction of the amino group of amino acids to the carbonyl group of N-acylsubstituted diketopiperazines [2], discovered by the authors, they have obtained di-exo-N-phthalylglycylglycine ethyl ester hydrate-2,5-dihydropyrazine (I), by interaction of 1,4-diphthalylglycyl-2,5-diketopiperazine with ethyl glycocol-late:

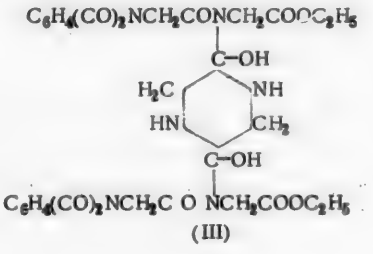


(I)

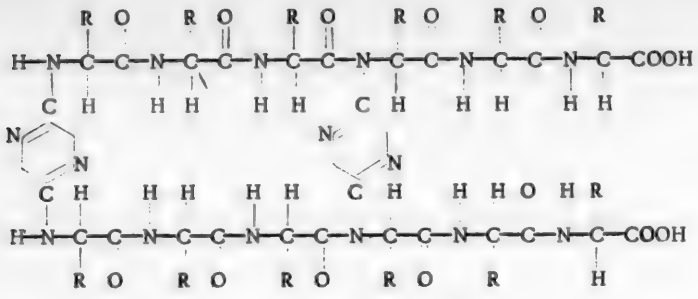
In addition to this compound, which was found to be the amidine derivative of diketopiperazine and phthalyldipeptide(glycylglycine), the acylated ethyl glycocollate was obtained. In this case the acyl group was phthalyl-glycine, which led to the formation of the phthalylglycylglycylic ester $C_6H_4(CO)_2NCH_2CONHCH_2COOC_2H_5$ (II).

As for the simplest N-acyldiketopiperazines, the endo-acyl group (phthalylglycyl-) was likewise regrouped to the exo-position and compound (III) was formed.

This synthesis confirmed the possibility of experimental realization of the structure proposed in 1947 by one of us (N.I. Gavrilov), since the compound obtained is found to be the central fragment (IV):



(III)



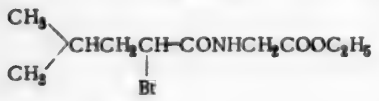
(IV)

In the carrying out of numerous investigations for the purpose of explaining the albumin structure and the possible binding of diketopiperazines with amino acids by nitrogen, Abderhalden and his co-workers used the amination reaction of dichloracyl derivatives of diketopiperazine by ammonia. Considering combinations of diketopiperazines with acyl halides to be the preliminary step for synthesis of N-aminoacyl derivatives of diketopiperazine, the authors synthesized a series of N-haloidacyl derivatives of diketopiperazine: N,N'-dichloracetyldiketopiperazine; N,N'-$\alpha$-dibromisocapryldiketopiperazine. Upon treatment of the above-enumerated compounds with ammonia, their decomposition was observed, with the formation of the amides of the amino acids and the diketopiperazine.

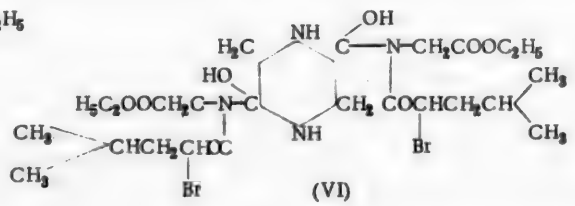
In one of our articles, the reactivity of N-acylated diketopiperazines was clearly demonstrated in the examples of N,N'-diacetyl- and N,N'-dichloracetyl-diketopiperazines. Their extraordinary lability was established with regard to the free amino groups and their ability to enter into reactions with bases, forming at the same time acylated amidines.

A detailed study of the interactions of N,N'-diacetyldiketopiperazine with glycocoll esters and other amino-acids,convinced us of the accuracy of the earlier-made assumption concerning synthesis of intermediate compounds of the amidine type. The deductions made in the case of N,N'-diacetyldiketopiperazine were confirmed by the reactions of N,N'-dichloracetyldiketopiperazine with amino acids.

In order to extend the earlier-made assumptions to include other N-acyldiketopiperazines, and by the same token to enlarge the circle of transformations studied, the authors synthesized 1,4-di-($\alpha$-bromnorcapryl)-2,5-diketopiperazine [3]. Upon reaction of the latter with ethyl glycocollate, the authors obtained bromnor-caprylglycine ethyl ester (V) and di-exo-N-dibrom-nor-caprylglycine ethyl ester hydrate-2,5-dihydropyrazine (VI).



(V)



(VI)

## EXPERIMENTAL

1. Condensation Reaction of N,N'-Diphthalylglycyldiketopiperazine with Glycocoll. a) Conjugation with glycocoll in water. 1 g of N,N'-diphthalylglycyldiketopiperazine was mixed with 0.31 g of glycocoll (2 moles) in alkaline solution (0.165 g NaOH). The solution was shaken on a rocker for 5 hours; no change occurred during this time. A drop of the solution contained unchanged crystals of the original substance under the microscope. After termination of reaction, the precipitate was filtered off and washed with water. The remaining precipitate (0.9 g) represented unchanged N,N'-diphthalylglycyldiketopiperazine (negative anhydride and ninhydrin reactions). Therefore in this instance the Bergmann reaction did not take place.

b) Conjugation with ethyl glycocollate in absolute ether medium. 5 g of N,N'-diphthalylglycyldiketopiperazine was mixed with 25 ml of absolute ether and 2.1 g of ethyl glycocollate in 25 ml of absolute ether. The precipitate did not dissolve. The solution was placed on a rocker to be mixed. After 7 days of reaction, the precipitate was filtered off and washed with absolute ether. The precipitate and filtrate were examined separately.

Into the ether filtrate, basic in reaction, was passed dry hydrogen chloride. The precipitate formed was filtered off and washed with ether. The weight of dried substance was 0.8 g. By analysis, the substance was found to be ethyl glycocollate hydrochloride (m.p. 145°, $NH_2$=10.04%).

The precipitate was treated with chloroform. The chloroform filtrate was concentrated in vacuo in the cold. The separated precipitate was filtered off and washed with absolute ether. The substance obtained dissolved readily in chloroform and in acetone. It was precipitated from chloroform by ether. M.p. 160°. Weight 1.65 g.

Purification of the substance. The precipitate was dissolved in hot water and filtered while hot. Upon standing at room temperature, a precipitate separated from the aqueous solution, which was filtered off and washed on the filter with water, alcohol and ether (it was soluble in the last two). Since the precipitate was not homogeneous under the microscope, it was treated again with methyl acetate. A small portion dissolved (needles), but the greater portion did not go into solution (flakes) when a sample was checked under the microscope. The filtrate was concentrated to a small volume, and a substance with m.p. 183° was separated from it. The precipitate did not dissolve in methyl acetate; it melted at 145°.

The aqueous filtrate and the mother liquor from the recrystallization was concentrated by heat in vacuo. Upon treating with methyl acetate, two substances were separated with melting points as indicated above. The compound with m.p. 183° was analogous in its properties to the above-described, as was the compound with m.p. 145°

The precipitate weighed 4.3 g after treatment with chloroform. This precipitate gave a picric reaction and a biuret of the tripeptide type upon standing with alkali. It was treated three times in a beaker with hot water. It was filtered off and washed on the filter with boiling water and alcohol. The precipitate now did not give an anhydride reaction, and the biuret reaction was, as before, of the tripeptide type. Therefore, by the appearance of the anhydride reaction for the isolated substance up to the point of treatment of the precipitate with hot water, and by its disappearance after treatment of the precipitate with hot water, the presence in the precipitate of free diketopiperazine can be judged. The substances isolated from this reaction were analyzed.

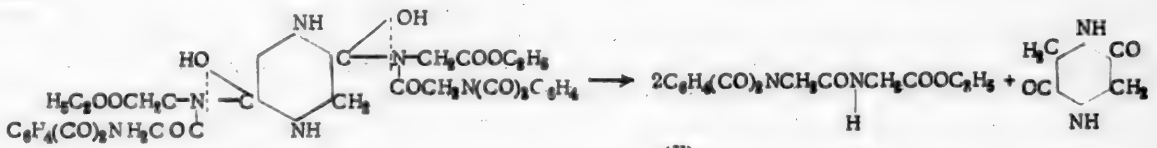
Analysis of the substance with m.p. 145° (I).

2.465 mg substance: 0.264 ml $N_2$ (25°, 734.4 mm). 3.015 mg substance: 5.185 mg $CO_2$; 1.296 mg $H_2O$. 3.027 mg substance: 6.130 mg $CO_2$; 1.294 mg $H_2O$. Found %: N 11.84; C 55.10, 55.27; H 4.95, 4.86. M 678.7 (Rast.). $C_{33}H_{34}O_{12}N_6$. Calculated %: N 12.11; C 55.33; H 4.899; M 694.

Analysis of the substance with m.p. 183° (II).

3.005 mg substance: 0.260 ml $N_2$ (19°, 734 mm). 2.960 mg substance: 6.276 mg $CO_2$; 1.293 mg $H_2O$. 2.975 mg substance: 6.310 mg $CO_2$; 1.292 mg $H_2O$. Found %: N 9.76; C 57.86, 57.88; H 4.89, 4.86. $C_{14}H_{14}O_5N_2$. Calculated %: N 9.65; C 57.93; H 4.83.

The separation of phthalylglycylglycine ethylester, and likewise the tracing of diketopiperazine by the anhydride reaction indicate a decomposition characteristic for all hydrate forms of amidines as per the following scheme:

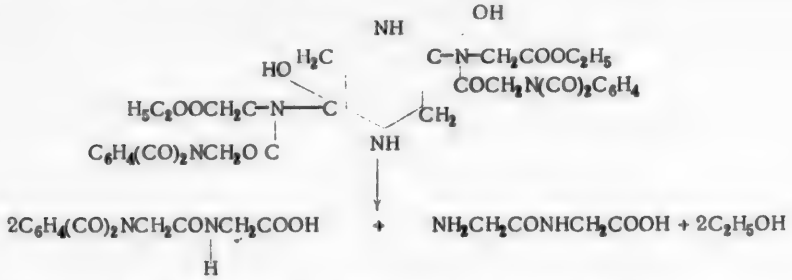


(I) (II)

Moreover, the presence of phthalylglycylglycine ethyl ester in the reaction products points to the fact that there also takes place a rearrangement of the acyl group from the endo- to the exo-position.

As proof of the rearrangement of the phthalylglycine group from the nitrogen position in the piperazine ring to the nitrogen of the side amino acid, arrangement was made to hydrolyze this compound with 1% hydrochloric acid with and without an enzyme. After standing for two days in a thermostatic bath, a precipitate separated from both solutions, which was found to be phthalylglycylglycine. For analysis the substance was recrystallized from

water. M.p. 229.5°. The complete absence of the anhydride and the biuret reactions, carried out with both $CuCl_2$ and $Co(NO_3)_2$, indicated that the substance isolated by the authors represented phthalylglycylglycine. The synthetic phthalylglycylglycine melted at 230° and did not give depression with the above-isolated substance. The decomposition scheme of the anilide in 1% HCl is cited below.



Diketopiperazine was not found. Its presence in this compound was demonstrated by the appearance in the filtrate of a ninhydrin reaction and a biuret of the dipeptide type. This experiment confirmed the assumption made earlier regarding the location of the phthalylglycine group on the nitrogen of the side chain.

2. Synthesis of 1,4-di-(α-bromnorcapryl)-2,5-diketopiperazine. 2 g of diketopiperazine was mixed with 11 g of α-brom-nor-caprylchloride [4]. Xylene (35 ml) was then added as the solvent and a few drops of thionyl chloride to speed the reaction. The mixture was heated on reflux in Wood's alloy at 138°. After 5-6 hours of boiling the strongly colored solution was filtered through a glass filter while still hot. The filtrate obtained was concentrated by heating in vacuo to an oily residue. To this residue in the flask was then added 100 ml of absolute ether. Upon prolonged standing (2-3 hours) in a cooling mixture a white crystalline powder precipitated, which was filtered off and washed with absolute ether. The substance was recrystallized from alcohol for analysis. M.p. 118°. Yield 4.5 g (instead of the theoretical 8.11 g).

In order to cut down on resinification, the experiments were carried out in benzene and toluene.

It is better to carry out the reaction with a stirrer. It was not possible to obtain 1,4-di-(α-brom-nor-capryl)-2,5-diketopiperazine in either the first or the second solvent.

It was observed that optimum conditions are: solvent – dry xylene, absence of thionyl chloride and preliminary stirring of the solution to avoid burning of the diketopiperazine which lies on the bottom of the flask.

8.500 mg substance: 0.481 ml $N_2$ (25°, 751 mm). 3.168 mg substance: 4.751 mg $CO_2$; 1.310 mg $H_2O$. 3.206 mg substance: 4.812 mg $CO_2$; 1.310 mg $H_2O$. Found %: N 6.04; C 40.93, 40.97; H 5.25, 5.21. $C_{16}H_{24}O_4N_2Br_2$. Calculated %: N 5.98; C 41.03; H 5.17.

3. Condensation of 1,4-di-(α-brom-nor-capryl)-2,5-diketopiperazine with Ethyl Glycocollate in Absolute Ether Medium. 1.1 g of dibrom-nor-capryldiketopiperazine was placed in a flask and 10 ml of absolute ether added. While stirring, 0.5 g of ethyl glycocollate in 10 ml of absolute ether was added. In the first ten minutes everything dissolved, but the solution was not transparent. Medium – weakly basic. The precipitate was filtered off rapidly and washed on the filter with absolute ether. The ether filtrate became turbid upon standing. The precipitate which separated from the ether filtrate was filtered off. Upon recrystallization from acetone, the diketopiperazine was obtained (50 mg), and the acetone filtrate gave an oil upon concentration. Weight 0.7 g.

Treatment of the ether filtrate. The ether filtrate was concentrated in vacuo in the cold to an oily residue which crystallized instantly. The separated substance was dissolved in a very small volume of benzene with heating, was cooled and precipitated by petroleum ether. The separated precipitate was filtered off and washed on the filter with petroleum ether. The dry precipitate weighed 0.6 g. Upon analysis, the precipitate was found to be the brom-nor-caprylglycine ethyl ester. M.p. 78°.

8.970 mg substance: 0.513 ml $N_2$ (24°, 751 mm). 3.055 mg substance: 4.816 mg $CO_2$; 1.800 mg $H_2O$. 3.050 mg substance: 4.800 mg $CO_2$; 1.800 mg $H_2O$. Found %: N 4.92; C 43.01, 42.94; H 6.59, 6.60. $C_{10}H_{18}O_3NBr$. Calculated %: N 5.0; C 42.86; H 6.43.

The precipitate from the ether filtrate was recrystallized from water. Melting point of the dried substance was 120°, soluble in methanol, chloroform, very readily in acetone, insoluble in water.

2.795 mg substance: 0.206 ml $N_2$ (18°, 740.5 mm). 3.020 mg substance: 4.719 mg $CO_2$; 1.325 mg $H_2O$. 3.160 mg substance: 4.932 mg $CO_2$; 1.330 mg $H_2O$. Found %: N 8.41; C 42.64, 42.59; H 6.20, 6.16. $C_{24}H_{42}O_8N_4Br_2$. Calculated %: N 8.31; C 42.73; H 6.23.

## SUMMARY


1. Di-exo-N-phthalylglycylglycine ethyl ester hydrate-2,5-dihydropyrazine amidine was obtained.

2. Di-exo-N-brom-nor-caprylglycine ethyl ester hydrate-2,5-dihydropyrazine was obtained.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# SPECTROPHOTOMETRY OF BIURET COMPLEXES AS A METHOD FOR THE INVESTIGATION OF ALBUMINS AND PEPTIDES

## XV. APPLICATION OF THE BIURET REACTION WITH NICKEL TO THE INVESTIGATION OF GELATIN HYDROLYSIS

M. I. Plekhan and E. N. Voluiskaya

Hydrolytic break-down of albumin substances and the investigation of their decomposition products is one o the first methods in attempting to understand the structure o albumin substances.

If the separation of individual compounds from albumin hydrolyzates offers difficulties, it is more difficult to determine through what phases disintegration of the albumin molecule passes. Up to the present time, chemical characterization of the process as a whole has been based principally upon change in nitrogen combinations. Attempts have been made to observe disintegration of the molecule with the help of the ultracentrifuge, by decrease in the molecular weight of the fragments. With regard to complete characterization of the overall variety of substances forming during the different phases of disintegration of albumin, the picture at the present is obscured if the final hydrolytic phases are not considered where reactions lead to a mixture of amino acids. It is apparent that each new method of investigation should be applied, and the reactions, to a partial if not complete clarification of this complex field.

Taking into account the considerations stated, we have utilized certain observations made upon nickel biuret complexes of the peptides, which were obtained earlier by the authors [1] in order to investigate gelatin hydrolysis under various conditions. Against the background of the tripeptide orange complex, and the yellow complexes of the peptides, with a longer chain, the nickel complex of the dipeptide differs markedly, not only in its blue color, but also in its absorption curve maximum.

During the process of albumin disintegration, it could be expected that the appearance of dipeptide and amino acid complexes should be accompanied by a characteristic change in color, and by a corresponding change in the absorption curve. The color of the albumin complex should change from orange to green and the absorption curve should exhibit a maximum at wave length $\sim$ 630 mμ. Speaking to the point, it has not been known up to the present time at which stage of disintegration dipeptides and amino acids appear. In our investigations we have endeavored to answer this question in the case of enzymatic acid and basic hydrolysis of gelatin. Before going into the direct investigation of albumin hydrolyzates, it was necessary to complete certain preliminary experiments: 1) quantitative determination of nickel in peptide complexes; 2) determination of how the absorption character of the nickel biuret complex of one peptide is changed if in the solution there appears the complex of a peptide of different chain length.

### 1. The Nickel Content of Biuret Complexes for Peptides.

Electrolytic determinations of nickel in peptide complexes led to the results cited in Table 1.

The colorimetric method [2] for determining nickel gave values close to those cited in Table 1, and can be substituted for the electrolytic method. In further experiments on hydrolyzate complexes, the authors have applied the colorimetric method for determining nickel. Results cited in Table 1 indicate that the nickel content is highest in the tripeptide orange complex.

Regarding the structure of the nickel biuret complexes of the peptides, the following can be said for the time being:

1) Upon subjecting the nickel complexes of peptides and albumins to the action of an electric current, the authors have observed that they are shifted toward the anode. Consequently, the colored portion of the complex belongs to anionic nickel and the organic portion of the complex is contained in the anion. Evidently the nickel biuret complexes of the peptides belong to the same group of higher complex compounds as the copper complexes. At present it is not clear just what coordination number nickel has in these complexes.

TABLE 1

| Name of substance | Quantity of substance (in mg/1 mg nickel) | Number of moles of substance per g-atom Ni | Number of of g-atoms of total nitrogen per g-atom Ni |
|---|---|---|---|
| Glycylglycine | 7.34 | 3.58 | 7.16 |
| Diglycylglycine | 4.1 | 1.26 | 3.78 |
| Triglycylglycine | 6.87 | 1.32 | 5.28 |
| Alanine | 60 | 40 | 40 |

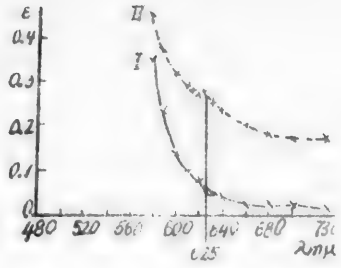



Fig. 1

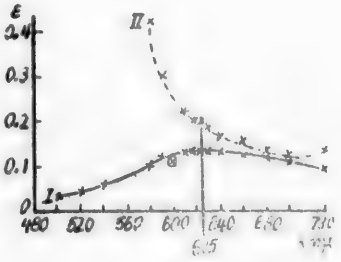



Fig. 2

2) In a series of complex peptides the most perfect is found to be the yellow biuret complex which is formed by the tetrapeptide and by peptides with a longer chain. The tetrapeptide is able to replace tripeptide and dipeptide from the nickel biuret complex. A tripeptide is only partially able to replace a dipeptide from its nickel biuret complex, which indicates the rather close similarity in activity in formation of tri- and di-peptides complexes.

2. Formation of nickel biuret complex in an environment of glycyl peptide mixtures.

In experiments with glycylic di-, tri- and tetra-peptides was determined the manner in which the absorption character changes if in a solution of one of the complexes there appears the complex of another peptide.

a) In a solution of tripeptide complex there appears a dipeptide complex. If glycylglycine dipeptide and hydrated oxide are added to a solution of diglycylglycine tripeptide complex (Fig. 1, curve I; Table 2, column I), then a change occurs after 1.5 hours, as shown by curve II, Fig. 1 (Table 2, colume II).

Comparing curve II with curve I, it can be noted that in curve II a maximum at wave length 625 mμ appears (the characteristic maximum for the dipeptide Ni-complex) and an increase in absorption intensity occurs in the region 600 to 730 mμ.

Therefore, the appearance of a dipeptide complex against a tripeptide complex background is characterized by the appearance of a maximum. Consequently, if dipeptides are going to appear in solution during the process of albumin disintegration, their presence can be detected by the appearance of a maximum in the curve. The authors will further demonstrate that actually such a phenomenon is observed under defined conditions during a given phase of albumin disintegration.

b) In a solution of dipeptide (glycylic) complex there appears a tripeptide (glycylic) complex. In a given experiment a blue solution of the nickel biuret complex of the dipeptide was prepared, which is characterized by curve I on Fig.2 and the data in Table 2, column III. To this solution was added a tripeptide and hydrated nickel oxide. The solution changed in color – it became orange. Spectrophotometric curve II, Fig 2; Table 2, column IV indicates that the course of the dipeptide complex (I) curve changed, the intensity of absorption raised sharply from 480 to 625 mμ; the curve resembles the one characteristic for the tripeptide complex, but along with this there is a maximum at wave length 625 mμ and an increase in the absorption intensity on the section from 625-730 mμ which is characteristic for the dipeptide complex.

c) In a solution of the tetrapeptide there appears a dipeptide complex. A solution of the tetrapeptide nickel biuret complex, canary-yellow in color, was prepared. The spectrophotometric curve for this solution is presented in Fig. 3, curve I, and by Table 2 data, column V. Dipeptide and hydrated nickel oxide were added to the solution, the coloration of the solution after 1.5 hours was hardly changed visibly, but the spectrophotometric curve displayed characteristic changes (curve II). In Fig. 3 it can be seen that curve II differs from curve I in that there appears a small maximum at wave length 615 mμ; absorption all along the spectrum is considerably increased, especially at wave lengths 580-730 mμ. The appearance of the dipeptide complex in a solution of tetrapeptide complex is evidently similar to the experiment with the tripeptide complex, i.e., there appears a maximum on a well-defined section of the wave length against the background of a curve which does not possess

a maximum. Moreover, the absorption in the range 560-730 mμ increases noticeably.

TABLE 2

Spectrophotometric Investigation of Nickel Biuret Complexes of Peptide Mixtures

| Wave length λ (in mμ) | Value for optical density, ε | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Tripeptide complex 0.034 M | Mixture of tripeptide 0.034 M and dipeptide 0.049 M complexes | Dipeptide complex 0.043 M | Mixture of dipeptide 0.043 M and tripeptide 0.04 M complexes | Tetrapeptide complex 0.05 M | Mixture of tetrapeptide 0.09 M and dipeptide 0.066 M complexes | Glycocoll complex 0.05 M | Mixture of glycocoll 0.05 M and tripeptide 0.03 M complexes |
| | I | II | III | IV | V | VI | VII | VIII |
| 480 | | | 0.039 | | | | 0.008 | |
| 500 | | | 0.033 | | | | 0.005 | |
| 520 | | | 0.046 | | | | 0.0125 | |
| 540 | | | 0.0505 | | | | 0.018 | |
| 560 | | | 0.083 | | 0.1551 | 0.241 | 0.0878 | |
| 580 | 0.3514 | 0.46 | 0.109 | 0.409 | 0.0520 | 0.1299 | 0.056 | 0.345 |
| 590 | 0.2174 | 0.371 | 0.122 | 0.308 | 0.0374 | 0.107 | 0.068 | 0.230 |
| 600 | 0.1350 | 0.32 | 0.112 | 0.275 | 0.0354 | 0.099 | 0.080 | 0.160 |
| 610 | 0.1061 | 0.292 | 0.133 | 0.222 | 0.0284 | 0.093 | 0.082 | 0.120 |
| 615 | 0.0970 | 0.286 | 0.1308 | 0.2104 | 0.0260 | 0.095 | 0.087 | 0.114 |
| 620 | 0.0833 | 0.272 | 0.133 | 0.199 | 0.0260 | 0.093 | 0.086 | 0.102 |
| 625 | 0.0578 | 0.28 | 0.137 | 0.204 | 0.0257 | 0.088 | 0.085 | 0.089 |
| 630 | 0.0566 | 0.25 | 0.136 | 0.187 | 0.0220 | 0.0823 | 0.089 | 0.082 |
| 640 | 0.0518 | 0.238 | 0.134 | 0.167 | 0.0190 | 0.086 | 0.085 | 0.070 |
| 660 | 0.030 | 0.20 | 0.127 | 0.155 | 0.020 | 0.075 | 0.077 | 0.050 |
| 680 | 0.0310 | 0.187 | 0.124 | 0.138 | 0.0129 | 0.068 | 0.061 | 0.041 |
| 700 | 0.0243 | 0.174 | 0.112 | 0.1203 | 0.0119 | 0.063 | 0.047 | 0.038 |
| 730 | 0.0160 | 0.171 | 0.095 | 0.130 | 0.0109 | 0.053 | 0.028 | 0.034 |

Fig. 3.

Fig. 4.

d) Formation of the nickel biuret complex from a mixture of glycylic tripeptide and glycocoll. Likewise examined was the effect of tripeptide complex formation in the presence of the amino acid of glycocoll. A solution of nickel sulfate was added to a mixture of the tripeptide and glycocoll in alkaline solution, and the spectrophotometric curve was photographed after a given lapse of time. The optical densities are cited in Table 2, colume VII. On Fig. 4 is pictured curve III corresponding to this solution. Here also is plotted curve II, corresponding to the nickel biuret complex of tripeptide, and curve I—to the complex of glycocoll. Curve IV represents an arithmetically-obtained sum, ε, of I and II curves. It can be seen that curve III coincides neither with curve IV nor curve II. This indicates that glycocoll under these conditions participates only partially in the reaction, by which is explained the higher absorption for curve III on the wave length section 615-730 mμ, as compared with curve II.

Moreover, the difference between curves III and IV indicates that the biuret complex of the tripeptide was completely formed, and that glycocoll reacted partially at the same time, possibly forming a new type of complex.

The experiments which have been described give some idea of the change in character of the absorption for a peptide complex when there appears in the solution a new peptide of different chain length.

Following are the principal observations.

1) Appearance of a dipeptide complex in a solution of tripeptide complex causes an intensification of absorption in the range 560-573 mμ, and especially at wave length 625-615 mμ, which is denoted on the curve by formation of a maximum.

2) Appearance of a dipeptide complex in a solution of tetrapeptide complex likewise leads to an increase in absorption at wave length 560-730 mμ.

3) Appearance of an amino acid in a solution of tripeptide complex causes a small increase in absorption at 560-730 mμ.

3. Investigation of Enzymatic Hydrolysis of Gelatin.

Gelatin solution (2%) was reacted with pepsin (0.2% solution) at 37°, pH = 1.5-2 for 245 hours. As indicators to characterize the process, the following were chosen: 1) total nitrogen content in test sample (by Kjeldahl); 2) free α-amino nitrogen content (according to Van Slyke); 3) the character of the light absorption by the nickel biuret complex (spectrophotometric determination of the biuret complex solution); 4) nickel content of the biuret complexes of each sample.

The analyses are summarized in Table 3 for enzymatic hydrolysis carried out for 245 hours duration.

TABLE 3

Enzymatic Hydrolysis of Gelatin Solution (2%) with Pepsin (0.2%) at 37°, pH = 1.5-2.0.

| Time from start of reaction (in hrs) | In 1 ml of sample | | | | Complex color |
|---|---|---|---|---|---|
| | Total nitrogen (in mg) | Amino nitrogen (in mg) | Content | | |
| | | | Ni (in mg) | in g-atoms $N_{tot.}$ / Ni | |
| 0 | 3.356 | 0.15 | 1.4 | 10:1 | Orange |
| 5 | 3.35 | 0.161 | 1.025 | 14:1 | Orange-yellow |
| 11 | 3.35 | 0.17 | 1.05 | 13:1 | Orange-yellow |
| 25 | 3.34 | 0.187 | 1.075 | 13:1 | Yellow |
| 49 | 3.34 | 0.32 | 0.9 | 16:1 | Yellow |
| 245 | 3.34 | 0.334 | 0.9 | 16:1 | Yellow |

It should be noticed that the amino nitrogen remained practically unchanged for 25 hours. At 49 hours the amino nitrogen doubled, and then remained constant for two hundred hours.

Judging from the data which indicated the free amino nitrogen change, the peptide combinations did not break during the first 25 hours. Before anything else there began a certain process of hydrolysis of peptide combinations at the expense of the acidity of the medium.

Color changes: at 25 hours the complex was yellow in color, which indicated the formation of complexes characteristic for longer chains than tripeptide. The nickel content of the complex decreases, as the data of Table 3 indicate, and the ratio between nitrogen atoms and nickel atoms increases.

The spectrophotometric investigation of the nickel biuret complexes from the enzymatic hydrolyzates are cited in Table 4 and Fig.5.

Fig. 5 indicates that with lapse of time there is observed a decrease in the intensity of absorption of the biuret complexes from sample to sample along the spectrum. After 49 hours the absorption intensity remains unchanged. A decreased intensity likewise indicates the formation of peptide complexes of longer chain than tripeptide. As was demonstrated earlier, nickel biuret complexes of peptides with longer chains than the tripeptide form yellow complexes possessing decreased absorption intensity in the range 580-730 mμ, as compared with the tripeptide orange complex. Changes in the absorption character by biuret complexes from the peptic digestion of gelatin indicate the formation of longer chains than tripeptide. And – what is especially important – the chain lengthening does not involve breaking of peptide combinations inasmuch as the free α-amino nitrogen remains almost unchanged.

TABLE 4

Spectrophotometric Investigation of the Nickel Biuret Complexes from the Enzymatic Hydrolysis of 2% Gelatin Solution

| Wave lengths λ (in mμ) | Value for optical density, ε | | | | | |
|---|---|---|---|---|---|---|
| | Sample 1 at 1 hr | Sample 2 at 5 hrs | Sample 3 at 11 hrs. | Sample 4 at 25 hrs. | Sample 5 at 49 hrs. | Sample 6 at 245 hrs. |
| 480 | | | | | | |
| 500 | | | | | | |
| 520 | | | | | | |
| 520 | | | | | | |
| 560 | | 0.3960 | 0.3275 | 0.3260 | 0.2580 | 0.3420 |
| 580 | 0.324 | 0.2260 | 0.1650 | 0.1647 | 0.1240 | 0.160 |
| 590 | 0.230 | 0.1651 | 0.1109 | 0.1090 | – | 0.090 |
| 600 | 0.173 | 0.1468 | 0.0809 | 0.0790 | 0.0570 | 0.0620 |
| 610 | 0.152 | 0.1313 | 0.0725 | 0.0666 | 0.0476 | 0.0586 |
| 615 | 0.146 | 0.1208 | 0.0630 | 0.0598 | – | 0.0403 |
| 620 | 0.136 | 0.1166 | 0.0598 | 0.0564 | – | 0.0376 |
| 625 | 0.129 | 0.1125 | 0.0630 | 0.0523 | 0.0353 | 0.0330 |
| 630 | 0.126 | 0.1080 | 0.0495 | 0.0510 | – | 0.0290 |
| 640 | 0.124 | 0.1070 | 0.0440 | 0.0440 | – | 0.0260 |
| 660 | 0.133 | 0.0898 | 0.0360 | 0.0377 | – | 0.0140 |
| 680 | 0.146 | 0.0808 | 0.0296 | 0.0303 | 0.0190 | 0.0120 |
| 700 | 0.157 | 0.0805 | 0.0294 | 0.0296 | – | 0.0120 |
| 730 | 0.167 | 0.0640 | 0.0273 | 0.0174 | – | 0.0145 |

Having in mind the structure of albumin as proposed by Gavrilov [3], such a process can be presented as follows: under the influence of the enzyme, diketopiperazine rings break off, the peptide chain lengthens to hexapeptide, which gives possibility for the formation of the yellow biuret complex. The ratio between total nitrogen and nickel should increase at this time, a fact which is confirmed by the analytical data cited in Table 3.

### 4. Investigation of the Alkaline Hydrolysis of Gelatin

Gelatin solution (2%) was reacted with 2% sodium hydroxide at 100° for 40 hours. Samples were taken at specific intervals and analyzed for total and amino nitrogen contents. Biuret complex solutions were made from each sample, which were spectrophotometrically analyzed for metal content in complex. The changes which are observed upon alkaline hydrolysis of gelatin are of different character in comparison to those described above for the enzymatic hydrolysis. The coloration of the complexes indicates an entirely different picture of disintegration. Table 5 includes the basic data obtained during the investigation. During the disintegration process the quantity of free α-amino hydrogen grows continuously being especially strong during the first 6 hours.

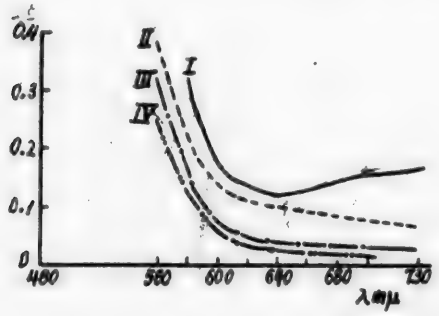



Fig. 5.

The nickel content in the complex slowly decreases during the first 2 hours, and then decrease in nickel proceeds more rapidly.

The results of the spectrophotometric investigation are cited in Table 6 and on Fig. 6.

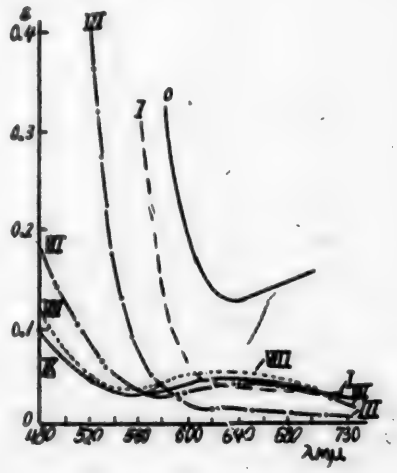



Fig. 6.

There are three phase changes apparent in the absorption character.

1) During the first 1.5 hours of hydrolysis a sharp decrease in absorption intensity occurs all along the

TABLE 5

Alkaline Hydrolysis of Gelatin Solution (2%) with 2% NaOH at 100°

| Time from start of reaction (in hrs) | In 1 ml of sample | | | | Complex color |
|---|---|---|---|---|---|
| | Total nitrogen (in mg) | Amino nitrogen (in mg) | Content | | |
| | | | Ni (in mg) | in g-atoms $N_{tot.}$ / Ni | |
| 0 | 3.26 | 0.19 | 1.4 | 10:1 | |
| 0.5 | 3.24 | 0.67 | 1.33 | 11:1 | Orange |
| 1 | 3.11 | 1.057 | 1.25 | 11:1 | Orange-yellow |
| 1.5 | 3.11 | 1.27 | 1.12 | 11:1 | Yellow |
| 2 | 3.11 | 1.36 | 1.05 | 12:1 | Yellow with green shade |
| 6 | 3.11 | 1.82 | 0.79 | 16:1 | Yellow-green |
| 14 | 3.11 | 1.92 | 0.62 | 20:1 | Green-yellow |
| 25 | 3.028 | 2.02 | 0.45 | 28:1 | Green |
| 30 | 3.028 | 2.58 | 0.75 | 17:1 | Green with blue shade |
| 40 | 3.028 | 2.58 | 0.67 | 19:1 | Green-blue |

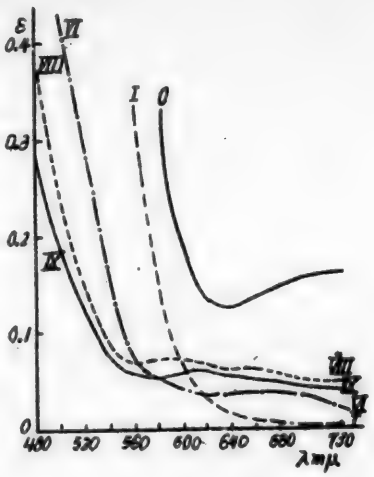



Fig. 7.

TABLE 6

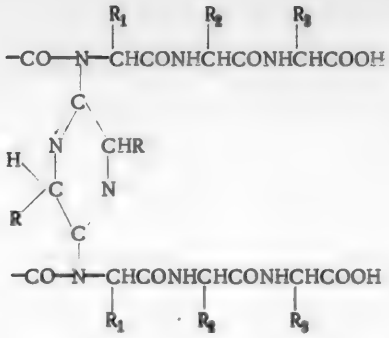
Spectrophotometric Investigation of the Nickel Biuret Complexes from the Alkaline Hydrolysis of 2% Gelatin Solution

| Wave lengths λ (in mμ) | Values for optical density, ε | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sample 0 at 0 hr | Sample 1 at 0.5 hrs. | Sample 2 at 1 hr. | Sample 3 at 1.5 hrs | Sample 4 at 2 hrs. | Sample 5 at 6 hrs | Sample 6 at 14 hrs | Sample 7 at 25 hrs | Sample 8 at 30 hrs | Sample 9 at 40 hrs |
| 480 | | | | | | | 0.2430 | 0.1720 | 0.117 | 0.094 |
| 500 | | | | | | 0.3067 | 0.1630 | 0.1203 | 0.075 | 0.058 |
| 520 | | | | 0.3990 | 0.3405 | 0.1860 | 0.1008 | 0.080 | 0.0475 | 0.042 |
| 540 | | | 0.3217 | 0.1650 | 0.2070 | 0.1110 | 0.0620 | 0.040 | 0.040 | 0.035 |
| 560 | | 0.3010 | 0.1507 | 0.0740 | 0.1030 | 0.0540 | 0.0480 | 0.0338 | 0.035 | 0.033 |
| 580 | 0.324 | 0.140 | 0.0770 | 0.0340 | 0.0470 | 0.0430 | 0.040 | 0.0299 | 0.045 | 0.035 |
| 590 | 0.230 | 0.0830 | 0.0450 | 0.0290 | 0.0430 | 0.0367 | 0.0453 | 0.0317 | 0.050 | 0.040 |
| 600 | 0.173 | 0.0620 | 0.0370 | 0.0250 | 0.0364 | 0.0330 | 0.0480 | 0.0330 | 0.051 | 0.045 |
| 610 | 0.152 | 0.0466 | 0.0337 | 0.0150 | 0.0272 | 0.0363 | 0.0490 | 0.0330 | 0.0525 | 0.048 |
| 615 | 0.146 | 0.0440 | 0.0334 | 0.0180 | 0.0236 | 0.0350 | 0.0458 | 0.030 | 0.053 | 0.046 |
| 620 | 0.136 | 0.0399 | 0.030 | 0.0179 | 0.0230 | 0.0380 | 0.0420 | 0.0290 | 0.052 | 0.043 |
| 625 | 0.129 | 0.0355 | 0.0220 | 0.0190 | 0.0234 | 0.0417 | 0.0430 | 0.0270 | 0.0515 | 0.043 |
| 630 | 0.126 | 0.0360 | 0.0190 | 0.0136 | 0.0222 | 0.0392 | 0.0410 | 0.0260 | 0.051 | 0.042 |
| 640 | 0.124 | 0.0354 | 0.0170 | 0.0133 | 0.0199 | 0.0350 | 0.0376 | 0.0240 | 0.050 | 0.041 |
| 660 | 0.133 | 0.0340 | 0.0120 | 0.0110 | 0.0213 | 0.0330 | 0.0390 | 0.0190 | 0.048 | 0.042 |
| 680 | 0.146 | 0.0360 | 0.0090 | 0.0091 | 0.0174 | 0.0340 | 0.0320 | 0.0167 | 0.043 | 0.0375 |
| 700 | 0.157 | 0.0306 | 0.0090 | 0.0094 | 0.0170 | 0.0274 | 0.0358 | 0.0188 | 0.036 | 0.031 |
| 730 | 0.167 | 0.0280 | 0.0070 | 0.0052 | 0.0178 | 0.0219 | 0.0285 | 0.0118 | 0.020 | 0.0205 |

spectrum. The color of the complex becomes yellow: formation of longer chains than tripeptides proceeds with a simultaneous sharp increase in the free α-amino groups. The disintegration involves breaking peptide combinations in the chain and in the rings according to the scheme: (see top of next page).

During this length of time the albumin molecule disintegrates. A mixture of fragments remains, which is probably quite homogeneous by the length of the peptide chain.

2) After 2 hours of hydrolysis there occurs a small maximum absorption at wave lengths 625-630 mμ. Absorption from 480 to 600 mμ is decreased, from 600-730 mμ it increases. The color of the complex acquires



(II)

(I)

a greenish shade, which indicates the appearance of the blue color complexes against the background of yellow complexes. The changes all-told undoubtedly indicate the appearance of chains of dipeptides in the hydrolyzate which should appear at the expense of tetrapeptide disintegration.

3) At 30 hours there is an intensive decrease in absorption at wave lengths from 480 to 600 mμ and a certain increase in absorption from 600 to 730 mμ. The absorption maximum is evidently getting brighter. The complex color is changing from green-yellow through yellow, acquiring a blue shade. By that time dipeptides already predominate in the hydrolyzate.

4) At 40 hours there is observed a decrease in absorption intensity all along the spectrum from 480 to 730 mμ. The complex color is green-blue. It is possible that at this stage the appearance of amino acids begins at the expense of dipeptide splitting. Alkaline hydrolysis at 100° shows altogether a strong disruptive action on the albumin molecule, which is indicated by the intensive increase in free α-amino nitrogen. Nevertheless, dipeptides appear only after 2 hours of hydrolysis, and amino acids at 40 hours. This is because the stability of the peptide combination varies according to the compound in which it finds itself.

5. Investigation of Acid Hydrolysis of Gelatin

Gelatin solution (2%) was hydrolyzed with 2% hydrochloric acid at 100° for 40 hours. In the time specified samples were taken which were analyzed for total and for amino nitrogen contents. The nickel biuret complex solutions were analyzed for nickel content in the complex, and the character of the light absorption was determined. The analytical results are cited in Table 7.

Table 7 shows that the amino nitrogen increases gradually during the first two hours, then at 30 hours the increase has become more intense, and after 30 to 40 hours of hydrolysis, free amino nitrogen continues to increase slowly.

The nickel content in the complex fluctuates somewhat, but has a general tendency to decrease.

The spectrophotometric results of investigation are cited in Table 8 and on Fig. 7. The character of the changes which develop during acid hydrolysis basically resemble the picture described for alkaline hydrolysis. However, there are some peculiarities.

1) During the first phase of acid hydrolysis a decrease in absorption is observed during the first hour, especially at wave lengths 690-730 mμ (Table 8). Absorption at 625 mμ reaches at that time its lowest value. In the alkaline hydrolysis experiment by that time (after 1 hour) the lowest absorption is likewise evident at 625 mμ, i.e., both in the case of alkaline as well as acid hydrolysis of gelatin, the maximum quantity of peptides capable of forming the yellow complex are present 1 hour from the start of the hydrolysis. Inasmuch as in this and the other case the process is accompanied by a continuous, intense increase in free amino nitrogen, apparently there is proceeding an energetic disruption of peptide bonds. At the same time, increase in amino nitrogen proceeds more intensely in the case of alkaline hydrolysis than in the case of acid hydrolysis. For the same time (1 hour) a greater quantity of free amino nitrogen is present in the sample from alkaline hydrolysis as compared with a sample at 1 hour from acid hydrolysis. But inasmuch as the intensity of the absorption by the nickel complexes of these two samples is very close, it should be assumed that in the case of acid hydrolysis disintegration proceeds not only with disruption of the peptide bond, but also without disruption (with splitting of the diketopiperazine rings).

2) After carrying out the acid hydrolysis for 1 hour, the decrease in absorption intensity by the complexes proceeds for wave lengths 480 to 600 mμ, with an increase in absorption intensity at wave lengths from 600 to 730 mμ. At the same time the decrease in absorption at short waves proceeds less vigorously than in the case of

TABLE 7

Acid Hydrolysis of Gelatin Solution (2%) with 2% HCl at 100°

| Time from start of experiment (in hrs) | Total nitrogen (in mg) | Amino nitrogen (in mg) | Content Ni (in mg) | Content in g-atoms $N_{tot.}$ / Ni | Complex color |
|---|---|---|---|---|---|
| 0 | 3.26 | 0.19 | 1.4 | 10:1 | |
| 0.5 | 3.17 | 0.44 | 0.95 | 15:1 | Orange |
| 1 | 3.17 | 0.63 | 0.8 | 17:1 | Orange-yellow |
| 1.5 | 3.1 | 0.65 | 1.12 | 12:1 | Orange-yellow |
| 2 | 3.09 | 0.68 | 1.2 | 11:1 | Yellow-orange |
| 6 | 3.04 | 1.047 | 1.2 | 11:1 | Yellow |
| 14 | 3.04 | 1.54 | 1 | 13:1 | Yellow with slight greenish shade |
| 25 | 3.04 | 1.83 | 1.07 | 12:1 | Yellow-green |
| 30 | 3.04 | 2.16 | 1.07 | 12:1 | Yellow-green |
| 40 | 3.04 | 2.25 | 0.56 | 24:1 | Green |

alkaline hydrolysis. However, the increase in absorption at wave lengths 600 to 730 m $\mu$ proceeds more vigorously in the case of acid hydrolysis. By this time the quantity of free amino nitrogen is higher in the sample from the alkaline hydrolysis.

The change in the absorption intensity of the complexes indicates that in both cases, i.e. in the acid and the alkaline hydrolysis processes for gelatin (after 1 hour for the acid and 1.5 hours for the alkaline), there begin to appear dipeptides in the hydrolyzate, according to which the increased intensity of absorption at 600-730 m$\mu$ is understandable. At the time in question the formation of dipeptides proceeds more rapidly in the case of acid hydrolysis.

In the case of alkaline hydrolysis, dipeptides appear as the result of splitting of tetrapeptides, which were formed during the first 1.5 hours of hydrolysis. In such case the appearance of blue complexes should proceed simultaneously with the disappearance of the yellow ones, i.e. intensification of absorption in the 600-730 m$\mu$ range should be accompanied by a considerable absorption decrease in the section 480-600 m$\mu$. The authors show in Fig. 6, curve VIII, that exactly just such a change in the absorption character takes place in the case of alkaline hydrolysis.

TABLE 8

Spectrophotometric Investigation of the Nickel Biuret Complexes from the Acid Hydrolysis of 2% Gelatin Solution

| Wave lengths λ (in m$\mu$) | Value of the optical density, ε | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sample 0 at 0 hr | Sample 1 at 0.5 hrs | Sample 2 at 1 hr | Sample 3 at 1.5 hrs | Sample 4 at 2 hrs | Sample 5 at 6 hrs. | Sample 6 at 14 hrs | Sample 7 at 25 hrs | Sample 8 at 30 hrs | Sample 9 at 40 hrs |
| 480 | | | | | | | | | 0.3877 | 0.2850 |
| 500 | | | | | | | 0.4313 | 0.3462 | 0.2516 | 0.2166 |
| 520 | | | | | | 0.420 | 0.2705 | 0.1680 | 0.1626 | 0.1345 |
| 540 | | | 0.4544 | 0.5149 | 0.4710 | 0.2345 | 0.1772 | 0.1099 | 0.0944 | 0.0786 |
| 560 | | 0.3320 | 0.2264 | 0.2615 | 0.2280 | 0.1070 | 0.0746 | 0.070 | 0.070 | 0.060 |
| 580 | 0.324 | 0.1460 | 0.1151 | 0.1356 | 0.1188 | 0.0591 | 0.0579 | 0.0599 | 0.0720 | 0.0270 |
| 590 | 0.230 | 0.0920 | 0.0678 | 0.0776 | 0.0737 | 0.0461 | 0.0530 | 0.0590 | 0.0740 | 0.0581 |
| 600 | 0.173 | 0.0550 | 0.0447 | 0.0578 | 0.0489 | 0.0335 | 0.0459 | 0.0654 | 0.0760 | 0.0646 |
| 610 | 0.152 | 0.0460 | 0.0317 | 0.0356 | 0.0454 | 0.0393 | 0.0460 | 0.0570 | 0.0734 | 0.0667 |
| 615 | 0.146 | 0.0350 | 0.0290 | 0.030 | 0.0408 | 0.0371 | 0.040 | 0.0609 | 0.0728 | 0.0701 |
| 620 | 0.136 | 0.0277 | 0.0217 | 0.0288 | 0.0399 | 0.0399 | 0.0372 | 0.0601 | 0.0716 | 0.0660 |
| 625 | 0.129 | 0.0250 | 0.0195 | 0.0204 | 0.0314 | 0 0317 | 0.0352 | 0.0572 | 0.0697 | 0.061 |
| 630 | 0.126 | 0.0150 | 0.0184 | 0.0167 | 0.0311 | 0.0305 | 0.0401 | 0 0564 | 0.0672 | 0.0582 |
| 640 | 0.124 | 0.0130 | 0.0153 | 0.0144 | 0.0285 | 0.0262 | 0.0380 | 0.0581 | 0.0655 | 0.0628 |
| 660 | 0.133 | 0.0071 | 0.0095 | 0.0155 | 0.0248 | 0.0180 | 0.0386 | 0.0601 | 0.0680 | 0.0570 |
| 680 | 0.146 | 0.0047 | 0.0102 | 0.0139 | 0.0207 | 0.0191 | 0.0401 | 0.0559 | 0.0607 | 0.0525 |
| 700 | 0.157 | 0.060 | 0.0104 | 0.0117 | 0.0226 | 0.0196 | 0.0382 | 0.0512 | 0.0560 | 0.0496 |
| 730 | 0.167 | 0.0620 | 0.0086 | 0.0130 | 0.0184 | 0.0202 | 0.0254 | 0.0360 | 0.0487 | 0.0466 |

Upon acid hydrolysis the appearance of dipeptides should proceed not only at the expense of tetrapeptides by splitting, but also at the expense of the free diketopiperazine rings which are split during the first hours of hydrolysis. Only in such cases will the appearance of blue complexes proceed without the simultaneous extensive decrease in the quantity of yellow complexes. In the acid hydrolysis from 1 hour to 30 hours, quite characteristic is the more significant increased absorption at the 600-730 mμ section than the decreased absorption in the 480-600 mμ range (Fig. 7, curve VIII).

3) After 30 hours for both the acid and alkaline hydrolysis of gelatin, the decreased absorption intensity by the biuret complexes is observed along the whole spectral section from 480 to 730 mμ (Fig. 6, curve IX; Fig. 7, curve IX).

Inasmuch as the absorption intensity by the amino acid complexes is considerably less than for the dipeptide, it is possible that a decrease in intensity of absorption in both cases can be explained by the appearance of amino acids at the expense of dipeptides which are disrupted.

Comparing with one another the results obtained from hydrolysis experiments on gelatin at various conditions, it can be seen that use of spectrophotometry of the nickel biuret complexes allows one to note the peculiarity of each process. The picture of these transformations, which undergo complex formation, and also the character of the absorption vary depending upon the conditions of hydrolysis.

No doubt this diversity should be connected with diverse chemical reactions. The old peptide theory of Hofmeister-Fischer cannot explain this diversity of reactions, since disruption of the molecule from the point of view of this theory should proceed only in the direction of shortening the chain.

The albumin molecule structural pattern proposed by a new theory of Zelinsky-Gavrilov [4], in spite of its probability and substantiation, is still for the time being a working hypothesis. Therefore, the schemes for disruption of the albumin molecule, which were cited by the authors in explaining the denoted changes in absorption character also represent only a working scheme.

## EXPERIMENTAL

Formation of Nickel Biuret Complex in Mixtures of Glycylic Peptides. Experiment a. A solution of of biuret Ni-complex of tripeptide was prepared. A weighed portion of tripeptide 0.0967 g was dissolved in 8 ml of water, 4 ml of KOH (2N) and 3 ml $NiSO_4$ (0.21 M). After one hour the excess hydroxide was filtered off. The solution was orange in color, and a spectrophotometric curve was taken (Table 2; Fig. 1, curve I). The spectrophotometry was carried out in a Koenig-Martens apparatus set-up [5]. Then to 13 ml of the same solution, a weighed portion of dipeptide, 0.0848 g was added and Ni introduced in the form of the hydroxide, the excess of which was filtered off after 1.5 hours standing. The color of the solution became lighter and the spectrophotometric curve was taken (Table 2; Fig. 1, curve II).

Experiment b. The biuret of the dipeptide Ni-complex was prepared. A weighed portion of the dipeptide, 0.0848 g was dissolved in 8 ml of water, 4 ml of KOH (2 N) and 3 ml of $NiSO_4$ (0.21 M). After standing 1.5 hours, the excess hydroxide was filtered off, and the solution had a blue color; the spectrophotometric curve was taken (Table 2; Fig. 2, curve I). To 12 ml of the same solution 0.0991 g of tripeptide was added, Ni was introduced in the form of its hydroxide. The solution turned from blue to orange. The spectrophotometric curve was taken (Table 2; Fig. 2, curve II).

Experiment c. The biuret complex of the tetrapeptide was prepared. A weighed portion of the tetrapeptide 0.1845 g, was dissolved in 10 ml of water, 4 ml of KOH (2 N) and 3 ml of $NiSO_4$ (0.21 M). After standing 1.5 hours the excess hydroxide was filtered off, and the color of the solution was yellow. The spectrophotometric curve was taken (Table 4; Fig. 4, curve I). To 12 ml of the same solution 0.0833 g of dipeptide was added, Ni was introduced in the form of its hydroxide. After standing 1.5 hours the excess nickel hydroxide was filtered off. Color of the solution remained yellow. The spectrophotometric curve was taken (Table 4; Fig. 4, curve II).

Experiment d. To a weighed portion of tripeptide, 0.0944 g, and of glycocoll, 0.0571 g, 9.5 ml of water, 3 ml of NaOH and 2.5 ml of $NiSO_4$ (0.21 M) were added. After standing 1.5 hours, the Ni hydroxide was filtered off, the color of the solution being orange. The spectrophotometric curve was taken (Table 4; Fig. 5, curve III).

Enzymatic Hydrolysis of Gelatin. 70 ml of water was poured over 4 g of gelatin for the night. On the following day, hydrochloric acid was added by indicator so that the pH = 1.5-2, and then 0.4 g of pepsin dissolved in 40 ml of NaCl (0.1%) was added, water, and again acid until pH = 1.5-2, so that the total volume of hydrolyzate was 200 ml. The experiment was carried out in a thermostatic bath at 37°.

During the experiment samples were taken after 5, 11, 25, 49 and 245 hours, in which were determined: total nitrogen according to Kjeldahl; amino nitrogen according to Van Slyke; the spectrophotometric curves of the nickel biuret complexes for each sample taken (Koenig-Martens apparatus), and the colorimetric determination of Ni in the biuret nickel complexes was carried out for each sample taken.

For amino nitrogen determination 1 ml samples were taken. For spectrophotometry and colorimetry the biuret complex was prepared in the following manner: to 6 ml of the sample of hydrolyzate was added 5.5 ml of water, 1.5 ml of NaOH (3 N) and 2 ml of $NiSO_4$ (0.21 M), and after 1.5 hours the Ni hydroxide precipitate was filtered off and the spectrophotometric curve was taken. Ni was determined colorimetrically in the same complex. The final result was reduced by recalculation to the quantity of Ni which was contained in 1 ml of the gelatin solution.

Alkaline Hydrolysis of Gelatin Solution. 100 ml of water was poured over 4 g of gelatin for the night. On the following day 100 ml of NaOH (4%) was added to the gelatin solution. The total volume was 200 ml. Hydrolysis was carried out on a water bath in a flask equipped with reflux condenser. During the experiment samples were taken after 30 minutes, 1, 1.5, 2, 6, 14, 20, 30 and 40 hours. In them was determined: amino nitrogen according to Van Slyke (samples from 2 to 0.5 ml); total nitrogen according to Kjeldahl; spectrophotometry of the biuret complexes of each sample was carried out and the Ni content of the complex was determined.

Acid Hydrolysis of Gelatin Solution. 100 ml of water was poured over 4 g of gelatin and left for the night. On the following day 100 ml of HCl (4%) was added. Hydrolysis was carried out at 100°.

During the experiment samples were taken after 30 minutes, 1, 1.5, 2, 6, 14, 25, 30 and 40 hours. Determined was: total nitrogen according to Kjeldahl, amino nitrogen according to Van Slyke; spectrophotometry of the Ni biuret complexes for each sample was carried out and Ni was colorimetrically determined in the complex.

## SUMMARY


1. The appearance of the nickel biuret complex of the dipeptide (glycylic) in a solution of the nickel biuret complex of the tripeptide (glycylic), and also in the solution of tetrapeptide (glycylic) causes intensification of absorption in the range 560-730 mμ. The absorption is particularly increased in the 615-625 mμ range, which is indicated on the curve in the form of a maximum.

2. In the case of enzymatic (peptic) hydrolysis of gelatin, the change in absorption character of the nickel biuret complexes of the hydrolyzates discloses an increasing quantity of peptides with chains longer than the tripeptide. The process proceeds without rupturing the peptide bonds.

3. At 40 hours of alkaline hydrolysis for gelatin, three basic phases were observed in the character change of absorption for the nickel biuret complexes:

a) During the first 1.5 hours, with intensive increase of α-amino nitrogen a sharp absorption decrease proceeds all along the spectrum, the color of the complex becoming yellow—all of which indicates the formation of longer chains than the tripeptide.

b) After two hours of hydrolysis there appears on the absorption curve a maximum at wave length 625-630 mμ; the absorption from 480 to 600 mμ decreases, from 600 to 730 mμ it increases. The color of the complex acquires a green shade. All of these changes indicate the appearance in the hydrolyzate of dipeptide chains. This process continues up to 30 hours.

c) After 30 hours decreased absorption intensity is observed all along the spectrum. The color of the complex is greenish-blue. At this stage the appearance of amino acids is possible.

4. During the process of acid hydrolysis of gelatin there are observed changes in the character of the absorption by the nickel biuret complexes, resembling in many ways the ones indicated for alkaline hydrolysis. The difference is contained in the following:

a) The formation of peptides with longer chain length than tripeptide proceeds, during the first stage of disintegration, in the case of acid hydrolysis, not only with liberation of α-amino nitrogen, but also without the rupture of peptide bonds, which is manifested by the same absorption intensity and smaller α-amino nitrogen content in the sample from acid hydrolysis.

b) The process of peptide formation, giving blue biuret complexes (dipeptides) begins in the case of acid hydrolysis after 1 hour and proceeds vigorously.

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# V. AROMATIZATION OF 2,3,3-TRIMETHYL-1-BUTENE WITH CHROMIUM CATALYSTS

R. D. Obolentsev and N. I. Kuvshinova

The literature on aromatization of alkenes, with principal chain length less than 6 carbon atoms, is very scant. In the papers of Goldwasser and Taylor [1,2], are reported the results of the aromatization of 2-methyl-2-pentene, 3-methyl-2-pentene, and 2-ethyl-1-butene with chromic oxide; i.e. alkenes with 5 carbon atoms in the principal chain. The data on the aromatization of alkenes with four atoms in the principal carbon chain is limited to the report on the two orientating experiments of the aromatization of 2,3,3-trimethyl-1-butene made by one of the authors in 1947 [3]. Knowledge on the aromatization of alkenes of this structure is of great interest in connection with the question of the mechanism of aromatization of aliphatic hydrocarbons not containing six or more carbon atom chains.

A. F. Plate [1] carefully examined the mechanism of the aromatization reaction of parafin hydrocarbons; but he did not concern himself with the question of the isomerization of alkenes, structurally of interest to the authors, during the aromatization. A. D. Petrov [4], reporting the dynamic formation of isoalkenes during polymerizations, likewise did not concern himself with the question of their formation during aromatizations, presupposing that it would be discussed in Plate's monograph.

The mechanisms, proposed by Rideal [5], Raik [6] for the aromatization of alkanes with 5 carbon atoms in the principal chain, can be extended for the aromatization of 2-ethyl-1-butene, 3-methyl-2-pentene, 2-methyl-2-pentene with chromium catalysts, if the formation of rings by means of the doublet index [6] is allowed. Such proposed mechanisms contain many shortcomings, which were pointed out for the aromatization of alkanes (carefully examined by Plate [1]). In support of their mechanisms, the above authors cite that such hydrocarbons as 2,3-dimethylbutane, i.e. alkanes with four carbon atoms in the principal chain, do not aromatize. The aim of the present investigation was to verify the previously discovered [3] aromatization of 2,3,3-trimethyl-1-butene, i.e., an alkene with four carbon atoms in the principal chain, and to study it in greater detail, if possible.

## EXPERIMENTAL

2,3,3-Trimethyl-1-butene (98.5 g) was prepared both from acetone and methanol by the method reported by one of the authors in a previous communication [7]. That obtained from the former, b.p. 77.5-78.5°; bromine number – 160.8; that obtained from the latter – b.p. 78-78.5°. Literature results: b.p. – 78°; bromine number – 163 [8];

Thermodynamic calculations, initially made in order to see if the isolated aromatization of 2,3,3-trimethyl-1-butene was thermodynamically feasible, showed that, at atmospheric pressure and 450-600°, this reaction would occur practically without reversal.

Experiments on the aromatization of 2,3,3-trimethyl-1-butene were conducted with two examples of chromium catalysts;

1) "chromic oxide on aluminum oxide", prepared by the simultaneous precipitation of chromic and aluminum hydroxides from a mixture of solutions of aluminate and chromate;

2) "chromic oxide", prepared by the reduction of ammonium bichromate with methanol followed by the precipitation of the hydroxide with ammonia solution.

The experiments were conducted in a continuous type apparatus with a "Pyrex" glass reactor. An analogous apparatus, as well as the experimental method, are reported in the previous communication [9].

The gaseous reaction products were either analyzed by means of a VTI apparatus, or were isothermally fractionated. The molecular weight (cryoscopic method) and the bromine number (Halpern and Vinogradova method [10]); the unsaturation, as mono-olefinic hydrocarbons, was calculated from these results. The aromatic hydrocarbons were determined by means of the specific and relative dispersion [11,12]. The saturated residue was determined by difference.

The results of the experiments on the aromatization of 2,3,3-trimethyl-1-butene are given in Tables 1-3. The materials balance of the experiments, as well as the yields of the hydrocarbons and the aromatics expressed as moles per 100 moles of the hydrocarbon used, are given in Table 1. The analytical results of the gaseous and liquid products evolved are given in Table 2.

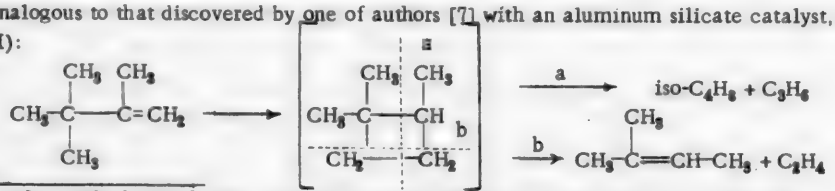
An examination of Table 1 shows that the number of moles of $\Sigma C_4H_8$, $C_4H_{10}$ is approximately equal to the number of moles of $\Sigma C_3H_6$, $C_3H_8$. In addition to butanes and butylenes, and propanes and propylenes in the gaseous products, hydrogen, methane, ethylene, and ethane are present in considerable amounts.

TABLE 1

Yield of liquid and gaseous products from experiments on the aromatization of 2,3,3-trimethyl-1-butene

| Conditions and experimental results | Catalyst and experiment number | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chromic oxide on aluminum oxide | | | Chromic oxide | | | |
| | 5 | 4 | 6 | 3 | 7 | 2 | 1 |
| Temperature °C | 580 | 580 | 530 | 580 | 580 | 550 | 510 |
| Rate of input (volume/volume of catalyst, in hours) | 3 | 1.2 | 3 | 3 | 1.6 | 1.0 | 1 |
| Duration of experiment (in min.) | 15 | 23 | 16 | 30 | 50 | 90 | 90 |
| Balance (in % by weight): | | | | | | | |
| gaseous products | 31.3 | 52.0 | 24.4 | 21.4 | 38.2 | 18.2 | 14.9 |
| liquid products | 37.8 | 10.7 | 63.9 | 74.1 | 50.0 | 63.6 | 72.7 |
| loss as coke* | 30.9 | 37.3 | 11.7 | 4.5 | 11.8 | 18.2 | 12.4 |
| Yield of gas (in moles per 100 moles of 2,3,3-trimethyl-1-butene): | | | | | | | |
| $\Sigma C_nH_{2n+2}$ | 76.6 | 110.2 | 35.8 | 28.8 | 85.6 | 30 | 29.6 |
| $\Sigma C_nH_{2n}$ | 29.8 | 23.9 | 17.8 | 22.1 | 39.0 | 16.3 | 3.2 |
| $\Sigma C_3H_6$, $n\text{-}C_4H_8$ | 15.6 | 11.2 | 8.2 | 10.8 | 17.1 | 6.6 | 2.0 |
| $\Sigma C_3$ | 15.6 | 13.5 | 10 | – | – | – | – |
| $\Sigma C_4$ | 18.8 | 14.3 | 10.8 | – | – | – | – |
| $H_2$ | 107.5 | 145.0 | 59.5 | 22.0 | 34.0 | 40.0 | 11 |
| $CH_4$ | 57.0 | 67.0 | 18.8 | – | – | – | – |
| $C_2H_6$ | 12.0 | 31.4 | 10.8 | – | – | – | – |
| $C_2H_4$ | 3.0 | 7.9 | 3.2 | 1.3 | 10.2 | 2.6 | 1.2 |
| $C_3H_8$ | 4.8 | 7.3 | 4.2 | – | – | – | – |
| $C_3H_6$ | 10.8 | 6.2 | 5.8 | – | – | – | – |
| $\Sigma C_4H_{10}$ | 2.8 | 4.5 | 2.0 | – | – | – | – |
| $n\text{-}C_4H_8$ | 4.8 | 5.0 | 2.4 | – | – | – | – |
| $iso\text{-}C_4H_8$ | 11.2 | 4.8 | 6.4 | 10.0 | 11.7 | 7.1 | 0.0 |
| Total yield of gas | 215 | 281 | 114 | 74 | 160 | 86 | 44 |
| Amount of 2,3,3-trimethyl-1-butene transformed (in mol. %) | | | | | | | |
| of $\Sigma C_3$, $C_4$** | 17 | 14 | 10 | – | 19 | – | – |
| of $\Sigma C_2$, $C_5$** | 15 | 39 | 14 | – | 31 | – | – |
| of aromatics | 8 | 6 | 5 | 8 | 13 | 10 | 4 |

The impression was created that the decomposition of 2,3,3-trimethyl-1-butene with chromic catalysts is analogous to that discovered by one of authors [7] with an aluminum silicate catalyst, i.e. according to the scheme (I):




(I)

* The method used for the experiments assured that the loss would not exceed 1%.

** See scheme (I)

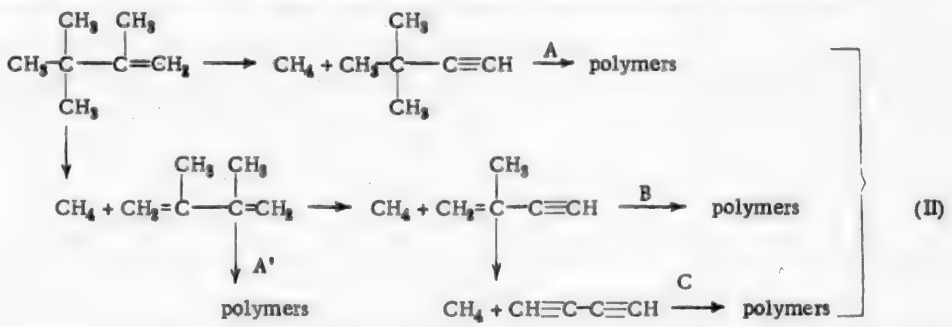
TABLE 2

Composition of liquid and gaseous products in experiments on the aromatization of 2,3,3-trimethyl-1-butene

| Conditions and experimental results | Catalyst and experiment number | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chromic oxide on aluminum oxide | | | Chromic oxide | | | |
| | 5 | 4 | 6 | 3 | 7 | 2 | 1 |
| Composition of the liquid products (in % by weight): | | | | | | | |
| unsaturated hydrocarbons | 76.1 | – | 79.3 | 90.0 | 74.4 | 85.0 | 93.0 |
| aromatic hydrocarbons | 20.9 | 50.7 | 7.5 | 10.0 | 24.6 | 15.0 | 5.0 |
| saturated residue | 3.0 | – | 12.2 | 0.0 | 0.8 | 0.0 | 2.0 |
| Composition of the gaseous products (in % by volume): | | | | | | | |
| $H_2$ | 50 | 51.6 | 51.9 | 30.3 | 21.4 | 46.3 | 25.3 |
| $C_2H_4$ | 1.4 | 2.8 | 2.8 | 1.8 | 6.4 | 3.0 | 2.7 |
| $C_3H_6$ | 5.0 | 2.2 | 5.8 | 14.6 | 6.9 | 7.6 | 4.6 |
| n-$C_4H_8$ | 2.2 | 1.8 | 2.1 | | 3.8 | | |
| iso-$C_4H_8$ | 5.2 | 1.7 | 5.6 | 14.0 | 7.3 | 8.3 | 0.0 |
| $CH_4$ | 26.6 | 23.6 | 16.5 | 38.8 | 35.7 | 34.9 | 67.4 |
| $C_2H_6$ | 5.6 | 11.2 | 9.5 | | 13.1 | | |
| $C_3H_8$ | 2.2 | 2.6 | 3.7 | | 3.4 | | |
| $\Sigma C_4H_{10}$ | 1.3 | 1.6 | 1.7 | | 1.3 | | |

The partyl isomerized decomposition products, [$C_4H_8$, $C_5H_{10}$], in all probibility in the presence of chromium catalysts [3] partly hydrogenate and partly dehydrogenate, which is fully possible thermodynamically [8].

The considerable formation of methane is explained by the large amount of demethanization of 2,3,3-trimethyl-1-butene followed by the polymerization of the products [see scheme(II)]. With this, a parallel dehydrogenation of the polymers during the polymerization occurs according to A,A', and B:




(II)

Table 1 shows the amount of coke formed (in % by weight) and amount of methane, expressed as moles per 100 moles of 2,3,3-trimethyl-1-butene used. If the demethanization proceeds according to the proposed outline, then the formation of one mole of methane must correspond to the following yield of coke, expressed in % by weight on the raw material used: A,A' – 0.835, B – 0.338, C – 0.170. Table 3 contains the yield of methane calculated on the yield of coke, as well as its true yield. The number of moles of hydrogen which is the difference between the sum: the hydrogen present plus that used for the hydrogenation of gaseous alkenes, and the hydrogen separating during the aromatization; i.e. the hydrogen obtained as a result of certain side dehydrogenations during the aromatization of a hundred moles of 2,3,3-trimethyl-1-butene is also given. This hydrogen is the product of the extensive dehydrogenation of polymers obtained by the polymerization and copolymerization of unsaturated compounds formed as a result of the demethanization of 2,3,3-trimethyl-1-butene. Some of the hydrogen and the coke could have been obtained from the dehydrogenation of isopentene, as well as from the intermediate products of the aromatization, and from the subsequent polymerization of the

dehydrogenation products and the intermediate products of the aromatization.

TABLE 3

Results of a characteristic demethanization of 2,3,3-trimethyl-1-butene and side dehydrogenation reactions

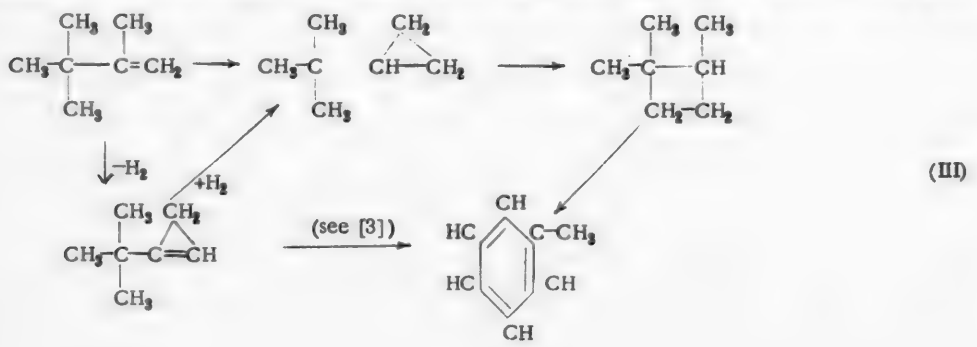
| Yields of the products (in moles per 100 moles of 2,3,3-trimethyl-1-butene used) | Catalyst and experiment number | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chromic oxide on aluminum oxide | | | Chromic oxide | | | |
| | 5 | 4 | 6 | 3 | 7 | 2 | 1 |
| $CH_4$ calculated from scheme (II), A,A' on the yield of the coke | 37 | 45 | 14 | 5 | 14 | 22 | 15 |
| The same from scheme (II), B | 92 | 110 | 35 | 13 | 35 | 54 | 37 |
| The same from scheme (II), C | 182 | 220 | 69 | 26 | 70 | 107 | 73 |
| Actual yield of $CH_4$ | 57 | 67 | 19 | – | 57 | >30 | >29.6 |
| Amount of $H_2$ from the side dehydrogenation | 103 | 170 | 62 | – | 24 | – | – |

According to Table 3, the actual yield of methane in experiment 7 occupies an intermediate position between the yield calculated from schemes (II), B and (II), C; and for experiments 4,5,6 – from schemes (II), A,A' and (II), B. The amount of hydrogen from the dehydrogenation is considerably higher in experiments 4,5,6 than in experiment 7. The amount of hydrogen in experiment 6 can be considered somewhat low, as the hydrogen used for the formation of the saturated hydrocarbons was not counted (Table 2). The relatively small amount of hydrogen in experiment 7, i.e. where the demethanization of 2,3,3-trimethyl-1-butene proceeds mainly by means of schemes (II), B and (II), C according to the amount of methane and the comparatively large amount in experiments 4,5,6, i.e., where the reaction proceeds mainly by means of schemes (II), A,A' and (II), B, are considered to be proof of the conclusion that the main part of the coke is formed as a result of the polymerization of the demethanization products, and the dehydrogenation of these polymers. Judging from the results of Mattox and Grosse [14], the formation of any substantial amounts of coke as a result of the condensation of the aromatics under the conditions of these experiments, is excluded.

Under these experimental conditions, the extent of the aromatization varied between 4 to 13 moles per 100 moles of 2,3,3-trimethyl-1-butene used, while the concentration of 'aromatics' in the liquid products varied from 5-50% by weight. One of the authors [3] has proposed an outline for the aromatization of 2,3,3-trimethyl-1-butene which provides for the formation of tert.-butylcyclopropene as an intermediate product.

N. Ya. Demyanov and M. I. Doyarenko-Demyanova [15] discovered that considerable amounts of coke and cyclopropene polymers were formed when cyclopropene was passed over $Al_2O_3$ at 380°. The authors proposed that, under these conditions, cyclopropene "does not isomerize to the allylene to any large extent". Therefore, it can be considered that, in the above experiment, the source of the coke and the polymers was the cyclopropene or its isomer, methylacetylene. Therefore, tert.-butylcyclopropene, the proposed intermediate product, or the corresponding acetylene derived from it, must be the source of the coke.

The results of the above experiments, which resulted in the proposed scheme for the decomposition of 2,3,3-trimethyl-1-butene by means of 2,3,3-trimethylcyclobutane, recall the fact that N. Ya. Demyanov [16] considered the derivatives of cyclopropane to be the intermediates between compounds with double bonds and cyclobutane derivatives, as well as the "means of increasing the ring by one carbon atom" open to them.




(III)

As a result of the views of N. Ya. Demyanov, it can be supposed that tert.-butylcyclopropene is transformed into tert.-butylcyclopropane by means of the hydrogen from the dehydrogenations, which increases its ring to 2,2,3-trimethylcyclobutane. The transformation of this derivative of cyclobutane into toluene can be explained in several ways; for example, the opening of the ring to form methylhexane or methylhexene, and then, aromatization [see scheme (III)]. This scheme appears to be a workable hypothesis; the question of the mechanism of the aromatization of 2,3,3-trimethyl-1-butene and similar hydrocarbons needs further study.

It must be pointed out that, on relatively long contact with chromic oxide under approximately the same conditions (Experiments 4 and 7), the aromatization proceeded more extensively than with chromic oxide on aluminum oxide; on short contact time, the extent of the aromatization is equal (Experiments 3 and 5). The extent and the method of decomposition is the same, but the yield of coke is 3 times larger with chromic oxide on aluminum oxide (Table 1); the latter is particularly interesting because the duration of Experiment 7 was 50 minutes, and Experiment 4 – 23 minutes. In accordance with scheme(I) and Table 3, it can be concluded that, under the conditions of Experiment 7, the demethylation of the molecules of 2,3,3-trimethyl-1-butene with "chromic oxide" proceeds by means of equations B and C, i.e., almost completely, while the side dehydrogenations develop relatively slowly. With chromic oxide on aluminum oxide a large decrease in the contact time (Experiments 4 and 5) leads to a considerable decrease of the decomposition of 2,3,3-trimethyl-1-butene, as well as a reduction in the side dehydrogenations; thus, the extent of the demethanization decreases. Decrease of the temperature to 50°, has an effect analogous to the decrease of contact time, but the decrease in the extent of the decomposition, dehydrogenation, and demethanization is relatively much greater. (Experiments 5 and 6).

## SUMMARY

Seven experiments on the aromatization of 2,3,3-trimethyl-1-butene with chromic oxide on aluminum oxide, and chromic oxide were conducted, which showed the following:

1) The aromatization of 2,3,3-trimethyl-1-butene proceeds to a relatively small extent; to 13% under the conditions used, but the fact of the aromatization itself shows that it is possible to aromatize hydrocarbons with four carbon atoms in the largest chain; the mechanism of this aromatization needs further investigating.

2) The main transformations of 2,3,3-trimethyl-1-butene with both catalysts appears to be its decomposition and demethanization, for which schemes(I) and (II) are proposed.

3) The secondary reactions are: a) dehydrogenation of the demethanization products and the decomposition of the intermediate products of the aromatization; b) the isomerization of isobutylene and the hydrogenation of the gaseous and liquid alkenes by means of the disproportionation of hydrogen.

4) The ability of chromium catalysts to effect the decomposition of 2,3,3-trimethyl-1-butene shows that they resemble aluminum silicate catalysts [7], in this way, and verify the conclusion made by one of the authors [3] that chromium catalysts can catalyze various transformation reactions of hydrocarbons in relation to fundamental reaction conditions.

The experimental part of the investigation was done with Zabulonov and Muzovskaya.

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# XXXIX. α-OXIDES AND SYNTHESIS OF A SERIES OF THIOPHENE COMPOUNDS

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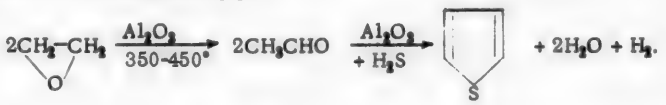
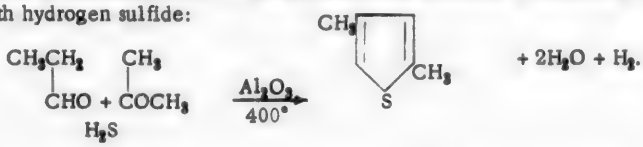
The reaction of ethylene oxide with hydrogen sulfide at 200°, in the presence of aluminum oxide, leads to six-membered saturated heterocycles with two heteroatoms in the 1,4-positions [1]; at higher temperatures (350-450°) – to thiophene [2,3]. The formation of thiophene is explained by the preliminary rearrangement of ethylene oxide into acetaldehyde, which then reacts with hydrogen sulfide by the well known reaction of A. E. Chichibabin [4]:



The reaction of ethylene oxide and hydrogen sulfide in contact with aluminum oxide at various temperatures was studied and it was found that the formation of thiophene already occurs at 300°; with increase in temperature the yield of thiophene increases and at 450° consists of 5.3% of the theoretical based on the ethylene oxide used in the reaction. According to the results of M. S. Malinovsky and B. N. Moriganov [2], the yield of thiophene at 450° is 6.5%.

It appeared interesting to see whether this reaction was general in character, i.e., can the homologs of ethylene oxide form homologs of thiophene under these conditions? In relation to propylene oxide it is known [5,6] that on contact with aluminum oxide it isomerizes to give a mixture of propionaldehyde and acetone.

In the present investigation it was shown that the reaction of propylene oxide with hydrogen sulfide in the presence of aluminum oxide at 400° leads to the formation of 2,4-dimethylthiophene. The formation of the latter can be explained only if the isomerization products of propylene oxide – acetone and propionaldehyde – reacted with hydrogen sulfide:



It was also found that 2,4-dimethylthiophene was formed even at 225° although in small amounts only. This appears to be a new fact upholding the rule found from the literature results that homologs of thiophene are formed more easily than thiophene itself [7].

## EXPERIMENTAL

### Reaction of ethylene oxide with hydrogen sulfide.

250°. 200 g of ethylene oxide was passed over $Al_2O_3$ in a stream of $H_2S$. 150 g of catalyzate was obtained (aqueous solution – 74.5 g; oil – 75.5 g). Upon the distillation of the aqueous and oily layer of the catalyzate were obtained: 1) 5.6 g of acetaldehyde [b.p. 20-22° (765 mm); m.p. of p-nitrophenylhydrazone – 128°]; 2) 3.4 g of 1,4-dioxane [b.p.100-101° (765 mm); $n_D^{20}$ 1.4216; $d_4^{20}$ 1.0322]; 3) 2.5 g of a fraction corresponding in boiling point to 1,4-thioxane [b.p. 52-55° (13 mm); $n_D^{20}$ 1.5052; $d_4^{20}$ 0.9910]; 4) 2.9 g of a fraction corresponding in boiling point to 1,4-dithiane [b.p. 95-115° (50 mm)].

300°. 113 g of catalyzate was obtained from 170 g of ethylene oxide (aqueous solution – 57 g; oil 56 g). Upon distillation were isolated: 5.3 g of acetaldehyde (b.p. 20-22°) and 5.8 g of a fraction, b.p. 70-93°.

Upon the redistillation of the fraction with b.p. 70-93° over sodium, 2.4 g of a substance with b.p. 81-83°, $n_D^{20}$ 1.5013, giving an indophene reaction with isatin and sulfuric acid, i.e. thiophene, was obtained. The α-chloromercurothiophene obtained from it melted at 182° after recrystallization from alcohol.

Literature results for α-chlormercurothiophene: m.p. 183° [8].

The yield of thiophene was 1.4% calculated on the ethylene oxide used in the reaction (4.3% of the weight of the oily layer of the catalyzate).

In addition, fractions corresponding in boiling point to the thioxane (2.4 g; b.p. 67-75° at 50 mm) and the dithiane (1.8 g; b.p. 100-120° at 50 mm).

350°. 110 g of catalyzate was obtained from 210 g of ethylene oxide (water −54 g; oil −56 g). Fractional distillation of the readily distillable substances of the aqueous and oily layers produced 5.5 g of a fraction with b.p. 80-90°, which, upon a subsequent redistillation over sodium, gave 4.1 g of thiophene; b.p. 82-84.5° (758 mm); $n_D^{20}$ 1.5166; $d_4^{20}$ 1.0690; melting point of the α-chloromercurothiophene (from alcohol) 183°.

The yield of the thiophene was 2.0%, based on the ethylene oxide used in the reaction and 7.2% of the weight of the oily layer.

400°. 92 g of catalyzate was obtained from 160 g of ethylene oxide (water −46 g, oil −46 g). 7.8 g of thiophene was obtained by fractional distillation over sodium; b.p. 82-84° (751 mm); $n_D^{20}$ 1.5209, $d_4^{20}$ 1.0620. Melting point of the α-chloromercurothiophene − 182-183°.

The yield of thiophene was 5.1% based on the ethylene oxide used in the reaction and 17% of the weight of the oily layer of the catalyzate.

450°. A turbid catalyzate was obtained from 220 g of ethylene oxide, which was distilled with super heated steam. The distillate was extracted with ether, and after the removal of the ether from the dried extract, the residue was fractionated. 11.2 g of thiophene with b.p. 83-84° (756 mm); $n_D^{20}$ 1.5236; $d_4^{20}$ 1.0490. Boiling point of the α-chloromecurothiophene −183°. The yield was 5.3% based on the ethylene oxide used.

Reaction of propylene oxide with hydrogen sulfide

400°. Propylene oxide (b.p. 34.5-35.0° at 753 mm) was passed over $Al_2O_3$ at a rate of 10 g per hour in a stream of $H_2S$. 200-250 g of propylene oxide was used in each experiment. 106 g of catalyzate was obtained from 212 g of the oxide (water −55 g, oil −51 g). On distillation of the oily fraction (dried with fused NaOH) from a flask with a column, the following fractions were obtained: (I) b.p. 100-125° −3.5 g; (II) b.p. 125-165° −23.5 g; (III) b.p. 165-250° −10.0 g; residue 12 g.

From Fraction II, upon redistillation through a column of 18 theoretical plates were separated: fraction with b.p. up to 136.5° − 3.5 g and a fraction with b.p. 136.5-139° (754 mm) −15.6 g. The latter had the odor of an aromatic hydrocarbon, did not give a reaction for sulfide or mercaptan, and, after redistillation once more over sodium had: b.p. 137.5-139.5° (750 mm); $n_D^{20}$ 1.5102; $d_4^{20}$ 0.9760.

After mercurating with mercuric chloride [6], separating the chloromercuro-compound, washing it with alcohol, and decomposing it with hydrochloric acid, 2,4-dimethylthiophene with the following constants was obtained: b.p. 138.5° (758 mm); $n_D^{20}$ 1.5150; $d_4^{20}$ 0.9899. The melting point of 5-chloromercuro-2,4-dimethylthiophene was 138°.

The literature results for 2,4-dimethylthiophene [9]: b.p. 138-139°; $d_{20}^{20}$ 0.9956; melting point of 5-chloromercuro-2,4-dimethylthiophene [10] −138-139°.

Found %: C 64.34, 64.38; H 7.74, 7.73; S 28.70, 28.67. $C_6H_8S$. Calculated %: C 64.23; H 7.20; S 28.56.

225°. 212 g of propylene oxide were used for the reaction. At the end of the reaction, a stream of nitrogen was passed in through a tube until the reaction products were completely removed and the temperature was increased 30°. 137 g of catalyzate was obtained (aqueous part −53 g, oil −84 g). The distillate of the water layer was dried and combined with the distillate of the oily catalyzate collected up to 190°.

Upon subsequent redistillation through a column of 18 theoretical plates, 4.3 g of a fraction with b.p. 47-135°, 9 g of a fraction with b.p. 135-141°, and 4.6 g of a fraction with b.p. 141-190° were obtained.

After redistillation of the fraction with b.p. 135-141° and distillation over sodium, 7.2 g of a fraction, with b.p. 138-140° (762 mm), $n_D^{20}$ 1.5033 and $d_4^{20}$ 0.9304, and which had an almost pure aromatic hydrocarbon odor, was obtained. The reaction for mercaptan was negative. The amount of sulfur (26.2%) was 2.35% lower than required for dimethylthiophene; the amount of carbon (66.06%) −2.2% higher.

From the reaction, analytical results, as well as the constants of the fraction obtained, it can be concluded that it consists of 2,4-dimethylthiophene along with another substance – apparently, a hydrocarbon.

The chloromercuro compound was obtained by mercuration; which, after washing with and recrystallization from alcohol, melted at 138°.

On mixed melting point determination with mercurated 2,4-dimethylthiophene obtained in the previous experiment, no depression was observed, and the mixture melted at 138°.

2,4-Dimethylthiophene (1.6 g) was obtained upon the decomposition of the chloromercuro compound with hydrochloric acid which, after distillation over sodium, had the following constants: b.p. 137-137.5° (755 mm); $n_D^{20}$ 1.5139; $d_4^{20}$ 0.9912.

Found %: C 64.25, 64.23; H 7.41, 7.38; S 28.60, 28.56. $C_6H_8S$. Calculated %: C 64.23; H 7.20; S 28.56.

## SUMMARY

It was shown that the reaction of propylene oxide with hydrogen sulfide over aluminum oxide at 400° leads to the formation of 2,4-dimethylthiophene, which can be explained by the initial isomerization of propylene oxide into acetone and propionaldehyde followed by the reaction of the mixture of the two with hydrogen sulfide.

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# THE SYNTHESIS OF 1,1-PHENYLCYCLOPENTANE CARBOXYLIC AND 1,1-PHENYLCYCLOPENTANE THIOCARBOXYLIC ACIDS AND SEVERAL DERIVATIVES

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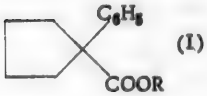
The synthesis of new spasmolytic substances of the type of alkylamino esters of disubstituted acetic esters occupies a considerable place in investigations of the past few years in the search for new medicinals. The changes in structure of the compounds synthesized for this purpose are extremely varied. Interesting modifications of the above type of spasmolytic substances appear to be alkylamino esters of alicyclic carboxylic acids, among which the esters of 1,1-phenylcyclopentane carboxylic acids (I) have attracted considerable attention from pharmacologists and clinicians because of certain peculiarities in its spasmolytic action.



(I)

Since esters of thiocarboxylic acids in many cases possess more clearly pronounced spasmolytic properties than those of the corresponding carboxylic acids, it appeared interesting to prepare several alkylamino esters of 1,1-phenylcyclopentane thiocarboxylic acid in order to investigate their pharmacological activity.

In order to prepare these compounds it was necessary to have 1,1-phenylcyclopentane thiocarboxylic acid as the starting material. According to the small number of papers in the literature [1], this acid is obtained by the condensation of 1,4-dibromobutane with benzyl cyanide in the presence of sodium amide followed by the saponification of the nitrile formed. The conditions for conducting each one of these reactions, as well as the properties of the 1,4-dibromobutane obtained, are varied. At the present time, 1,4-dibromobutane, for the most part, is obtained by the reaction of hydrogen bromide with tetrahydrofuran [2]. The authors repeated the methods given in the literature for conducting this reaction, and the most convenient method was shown to be the recommended prolonged heating of tetrahydrofuran with 48% hydrobromic acid. However, in this case the yield of 1,4-dibromobutane was inconsistant and lower than that reported in the literature. Considerably better results were obtained by adding sulfuric acid to the 48% hydrobromic acid and heating the tetrahydrofuran with a mixture of these acids. In this case 1,4-dibromobutane is obtained in a consistant and higher yield (70% of the theoretical). Toluene was used as the solvent for the condensation of 1,4-dibromobutane with benzyl cyanide instead of ether or liquid ammonia as given in the literature.

The saponification of 1,1-phenylcyclopentane nitrile was satisfactorily [1] effected by heating it with alcoholic alkali at atmospheric pressure, wherein 1,1-phenylcyclopentane carboxylic acid was obtained in a yield of 45.8 %. It is recommended that the heating be done in an autoclave at higher pressures; under these conditions phenylcyclopentane carboxylic acid is obtained in a yield of 95%.

The sodium salt and the acid chloride, whose constants were determined, were prepared from 1,1-phenylcyclopentane carboxylic acid.

The transformation of 1,1-phenylcyclopentane carboxylic acid to the corresponding thio-acid was effected by the action of an alcoholic solution of potassium hydrosulfide on the phenylcyclopentane carboxylic acid chloride. An excess of potassium hydrosulfide had to be used because in some cases a side reaction of the potassium salt of the thio-acid with the unreacted acid chloride to form the sulfide occurred.

1,1-Phenylcyclopentane thiocarboxylic acid is a crystalline, stable enough substance. In addition to its two alkylamino esters, the following common derivatives were obtained: potassium salt, disulfide, and ethyl ester.

## EXPERIMENTAL

1,4-Dibromobutane. 1530 ml of 48% hydrobromic acid was placed in a 2-liter three-necked flask equipped with mechanical stirrer, reflux condenser, thermometer immersed in the liquid, and dropping funnel; in small portions with stirring, 307 ml of concentrated sulfuric acid was carefully added to it. 172 g of tetrahydrofuran was added stepwise from the dropping funnel to the mixture of the acids, and heating on the oil bath was begun; at 62-68° inside the flask, the liquid began to boil, and in relation to the development of the reaction, the boiling point of the liquid gradually increased; when it reached 100-105°, the heating was continued at this temperature for 20-23 hours.

Upon cooling, the reaction mixture was transferred to a separatory funnel, the lower layer containing the 1,4-dibromobutane, was separated, and the upper layer – the acids – was extracted with chloroform. The chloroform extracts were combined with the 1,4-dibromobutane, and the chloroform solution washed, first with a 10% sodium bicarbonate solution, and then with water. After drying with calcium chloride, the chloroform was removed, and the 1,4-dibromobutane vacuum distilled. B.p. 85-90° at 15 mm. Yield 365 g (70% of the theoretical).

1,1-Phenylcyclopentane carboxylic acid nitrile. 87 g sodium amide in 1300 ml of absolute toluene, was placed in a flask equipped with a stirrer, reflux condenser, thermometer immersed in the liquid, and dropping funnel; 109.3 g of benzyl cyanide was added in small portions with continuous stirring (so that the temperature did not rise above 35°) to the suspension. The reaction mixture, which turned red, was stirred for 5-10 min. until the temperature decreased to 20-25°, then 200 g of 1,4-dibromobutane was added from the dropping funnel at such a rate that the temperature of the reaction mixture did not exceed 50-55°. After the addition of the 1,4-dibromobutane, the flask with the reaction mixture was heated on the water bath to 90-92° inside the liquid for 24 hours, after this the reaction mass was cooled, and small portions of water were added until the sodium bromide formed dissolved completely; two layers formed. The toluene layer was separated in a separatory funnel, and the water layer was completely extracted with toluene. The combined toluene solutions were washed with water and then dried with sodium sulfate. The toluene was removed in vacuum; the residual nitrile was vacuum distilled two times. A fraction with b.p. 110-170° at 25-30 mm was collected during the first distillation. 140 g was obtained. On redistillation, a fraction with b.p. 145-160° at 25-30 mm was collected 110 g (70% of the theoretical) was obtained.

1,1-Phenylcyclopentane carboxylic acid. 450 ml of a 20% solution of potassium hydroxide in methyl alcohol and 80 g of twice distilled 1,1-phenylcyclopentanecarboxylic acid nitrile were placed in a rotary autoclave, 1 liter capacity. The autoclave was closed, and the heating was begun with the rotation of the autoclave; the temperature inside the autoclave was gradually increased to 195-200°, and at this temperature, the agitation of the autoclave by means of its rotation was continued for 6 hours; the pressure inside the autoclave increased to 35-40 atm. After 6 hours the heating was stopped; when the autoclave cooled to room temperature, the ammonia was released, the autoclave was opened, the reaction mixture transferred to a Wurtz flask, and the alcohol was distilled off. The residue was dissolved in 500 ml of water and acidified with 240-250 ml of hydrochloric acid (1:1) until acid to Congo. The precipitated acid was filtered on a Buchner funnel, and washed with water; 84 g of impure 1,1-diphenylcyclopentane carboxylic acid with m.p. 157-158° (95% of the theoretical) was obtained. To obtain a sample for analysis, the 1,1-phenylcyclopentane carboxylic acid was recrystallized once from alcohol; m.p. 159°.

The sodium salt of 1,1-phenylcyclopentane carboxylic acid was obtained by treating 12 g of the acid with a saturated aqueous solution of 4.41 g of sodium bicarbonate. It was a colorless crystalline substance which crystallized from ethyl acetate in the form of needles. It melted above 220°.

0.3535 g substance: 0.1178 g $Na_2SO_4$. Found %: Na 10.84. $C_{12}H_{13}O_2Na$. Calculated %: Na 10.79.

1,1-Phenylcyclopentane carboxylic acid chloride. 50 g of 1,1-phenylcyclopentane carboxylic acid and 160 g of thionyl chloride were placed in a round bottomed flask equipped with a reflux condenser and heated to reflux on the water bath for 6 hours. The excess thionyl chloride was then removed, and the residue was vacuum distilled. A fraction with b.p. 149-150° at 20-23 mm was collected.

6.041 mg substance: 4.144 mg AgCl. Found %: Cl 16.97. $C_{12}H_{13}OCl$. Calculated %: Cl 17.02.

Potassium salt of 1,1-phenylcyclopentanethiocarboxylic acid. A solution of potassium hydrosulfide, obtained by saturating a solution of 25.3 g of potassium hydroxide in 14 ml of water and 447 ml of ethyl alcohol with hydrogen sulfide at –5° (until a weight increase of 22.4 g), was placed in a three-necked flask equipped with a stirrer, thermometer, reflux condenser, and dropping funnel. A solution of 44.7 g of 1,1-phenylcyclopentane carboxylic acid chloride in 350 ml of dry benzene was added stepwise at 5° to the above solution of potassium hydrosulfide. The mixture was stirred at this temperature for 20-30 min., filtered, and the solvents removed from the filtrate in vacuum (alcohol, benzene, water). The oily residue crystallized when absolute ether was added to it. After washing the crystalline substance with ether and its recrystallization from ethyl acetate, an almost colorless substance, with m.p. 166-167, readily soluble in water, was obtained. Yield 65-70% of the theoretical.

0.1061 g substance: 0.0998 g $BaSO_4$. 0.2157 g substance: 0.2050 g $BaSO_4$. Found %: S 12.91, 13.05, $C_{12}H_{13}OSK$. Calculated %: S 13.1.

1,1-Phenylcyclopentane thiocarboxylic acid. The potassium salt of 1,1-phenylcyclopentane thiocarboxylic acid was dissolved in water, the aqueous solution was filtered, and the free 1,1-phenylcyclopentane thiocarboxylic acid separated on the addition of 10% hydrochloric acid; after recrystallization from alcohol, colorless needles with m.p. 43-44°, soluble in alcohol, ethyl acetate, ether, and insoluble in water were obtained. Yield – 85% of the theoretical based on the potassium salt used.

4.017 mg substance: 10.280 mg $CO_2$; 2.418 mg $H_2O$. 0.2026 g substance: 0.2260 g $BaSO_4$. Found %: C 69.79; H 6.73; S 15.31. $C_{12}H_{14}OS$. Calculated %: C 69.65; H 6.76; S 15.4.

Sulfide of 1,1-phenylcyclopentane thiocarboxylic acid $C_5H_8(C_6H_5)CO{-}S{-}CO(C_6H_5)C_5H_8$. A solution of potassium hydrosulfide, prepared by saturating a solution of 5.5 g of potassium hydroxide in 100 ml of alcohol and 3 ml of water with hydrogen sulfide at –5° until a 5-6 g weight increase, was placed in a three-necked flask equipped with a stirrer, thermometer, reflux condenser, and dropping funnel. 11 g of 1,1-phenylcyclopentane carboxylic acid chloride in 30 ml of benzene was added stepwise to the above potassium hydrosulfide solution and the stirring at –5° was continued for 30 min. more. The precipitate, consisting of potassium chloride and the sulfide of the thioacid, was filtered and carefully washed free of the potassium chloride with water. The part insoluble in water was recrystallized from ethyl acetate. The colorless, shiny, crystals with m.p. 113-114° were insoluble in water and ether, and soluble in alcohol.

3.800 mg substance: 10.658 mg $CO_2$; 2.380 mg $H_2O$. 0.2290 g substance: 0.1432 g $BaSO_4$. Found %: C 76.49; H 7.00; S 8.58. $C_{24}H_{26}O_2S$. Calculated %: C 76.2; H 6.87; S 8.52.

Disulfide of 1,1-phenylcyclopentane thiocarboxylic acid. 3 g of 1,1-phenylcyclopentane thiocarboxylic acid was dissolved in the cold in 90 ml of ethyl alcohol. Concentrated hydrochloric acid was added stepwise to the above solution until acid to Congo, and an alcoholic solution of $FeCl_3$ was added stepwise. An almost colorless precipitate formed in the reaction mixture on rubbing with a rod, which was filtered, washed with water, and recrystallized from a mixture of ethyl acetate and alcohol. 1.5 g of a disulfide with m.p. 82-83.5° was obtained in the form of colorless crystals insoluble in water and soluble in alcohol and acetone.

3.079 mg substance: 7.934 mg $CO_2$; 1.670 mg $H_2O$. 3.431 mg substance: 8.858 mg $CO_2$; 1.936 mg $H_2O$. 0.2239 g substance: 0.2540 g $BaSO_4$. 0.2120 g substance: 0.2427 g $BaSO_4$. Found %: C 70.28, 70.41; H 6.07, 6.31; S 15.57, 15.71. $C_{24}H_{26}O_2S_2$. Calculated %: C 70.24; H 6.34; S 15.60.

Ethyl ester of 1,1-phenylcyclopentane thiocarboxylic acid. 8 g of the potassium salt of 1,1-phenylcyclopentane thiocarboxylic acid, 22.5 g of ethyl iodide, and 150 ml of absolute alcohol were placed in a round-bottomed flask equipped with a reflux condenser. The mixture was heated on the water bath to the boiling temperature of alcohol for 5 hours. The precipitated potassium iodide was filtered, and the alcohol and excess ethyl iodide were removed. The residue was dissolved in ether, the ether solution was washed with water, dried with sodium sulfate, and the ether removed. The residue was vacuum distilled. The ethyl ester of the thioacid was a thick, colorless liquid with b.p. 134° at 3-4 mm.

4.980 mg substance: 13.043 mg $CO_2$; 3.311 mg $H_2O$. 0.2302 g substance: 0.2301 g $BaSO_4$. Found %: C 71.43; H 7.44; S 13.72. $C_{14}H_{18}OS$. Calculated %: C 71.79; H 7.68; S 13.67.

Hydrochloride of the diethylaminoethyl ester of 1,1-phenylcyclopentane thiocarboxylic acid. 1.35 g of the potassium salt of 1,1-phenylcyclopentane thiocarboxylic acid and 40 ml of absolute ethyl alcohol were placed in a round-bottomed flask connected with a reflux condenser. 0.8 g of freshly distilled diethylaminoethyl chloride was added to the solution. The mixture obtained was heated on the water bath for 4 hours at 45° (bath temperature); at the end of the reaction, the potassium chloride precipitate was separated and the alcohol vacuum distilled. The residual oily substance was heated in vacuum on the water bath for 1 hour to remove the traces of unreacted diethylaminoethyl chloride, and then dissolved in ether. The solution was washed with water and dried with anhydrous sodium sulfate, filtered, and an ether solution of hydrogen chloride was added to the filtrate until acid to Congo. An almost colorless substance separated, which, after recrystallization from ethyl acetate, melted at 137-137.5°.

The hydrochloride of diethylaminoethyl thioester is readily soluble in water, alcohol, and acetone, and difficultly soluble in ethyl acetate, benzene, and insoluble in ether.

4.049 mg substance: 9.423 mg $CO_2$; 3 010 mg $H_2O$. 3.018 mg substance: 7.008 mg $CO_2$; 2.287 mg $H_2O$. 5.905 mg substance: 1.54 ml 0.01 N $H_2SO_4$ 6.187 mg substance: 1.80 ml 0.01 N $H_2SO_4$. 0.2170 g substance: 0.1483 g $BaSO_4$. 0.1802 g substance: 0.1228 g $BaSO_4$. 6.052 mg substance: 2.633 mg AgCl. 4.690 mg substance: 2.000 mg AgCl Found %: C 63.16, 63.33; H 8.28, 8.29; N 4.13, 4.07; S 9.38, 9.35; Cl 10.76, 10.55. $C_{18}H_{27}OSN \cdot HCl$. Calculated %: C 63.25; H 8.19; N 4.10; S 9.37; Cl 10.40.

Hydrochloride of the diethylaminopropyl ester of 1,1-phenylcyclopentane thiocarboxylic acid. 7.5 g of the potassium salt of 1,1-phenylcyclopentane thiocarboxylic acid, 7 g of diethylaminopropyl chloride hydrochloride, and 200 ml of absolute alcohol were placed in a round-bottomed flask connected with a reflux condenser. The mixture was heated to the boiling of the alcohol on the water bath for 3 hours. The precipitated potassium chloride was filtered, and the alcohol was removed from the filtrate in vacuum. The residue, the hydrochloride of the alkylamino thioester, was purified by converting it to the free base. A sodium bicarbonate solution was added to the hydrochloride, and the oil which separated, was extracted with ether. The ether solution of the alkylamino base was washed with water, dried with potassium carbonate, and the ether removed. The residual oil-like substance was heated on the water bath in vacuum for 1 hour in order to remove the traces of unreacted diethylaminopropyl chloride, and then dissolved in absolute ether. The ether solution was filtered, and an ether solution of hydrogen chloride was added to the filtrate, whereupon the hydrochloride of the diethylaminopropyl ester of 1,1-phenylcyclopentane thiocarboxylic acid separated which, after recrystallization from a mixture of alcohol and ethyl acetate, melted at 132-133°.

The hydrochloride of the alkylamino ester is readily soluble in water and in alcohol, poorly soluble in ethyl acetate, and insoluble in ether.

3.471 mg substance: 8.157 mg $CO_2$; 2.621 mg $H_2O$. 3.860 mg substance: 9.122 mg $CO_2$; 2.926 mg $H_2O$. 7.595 mg substance: 0.270 ml $N_2$ (23.5°, 733.0 mm). 6.675 mg substance: 0.249 ml $N_2$ (21.5°, 734.0 mm). 0.1347 g substance: 0.0880 g $BaSO_4$. 0.1638 g substance: 0.1086 g $BaSO_4$. Found %: C 64.09, 64.45; H 8.45, 8.48; N 3.96, 4.17; S 8.97, 9.10. $C_{19}H_{29}ONS \cdot HCl$. Calculated %: C 64.13; H 8.43; N 3.93; S 9.00.

## SUMMARY

1. Improved methods for the preparation of 1,4-dibromobutane, 1,1-phenylcyclopentane carboxylic acid, and its acid chloride are reported.

2. 1,1-Phenylcyclopentane thiocarboxylic acid, its usual derivatives, and some dialkylaminoalkyl esters were prepared.

## LITERATURE CITED

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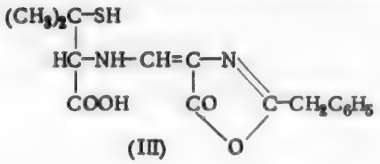
## IV. INVESTIGATION OF THE PRODUCTS OF THE CONDENSATION OF CYSTEINE AND 4-ETHOXYMETHYLEN-2-PHENYL-5-OXAZOLONE

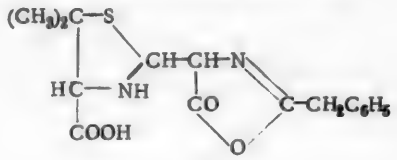
I. T. Strukov

Certain investigators, concerned with the solution of problems on the preparation of synthetic penicillin, have looked upon the thiazolidine-oxazolone structure (I) [1] as the intermediate compound in the process of formation of the antibiotic. For this reason many unsuccessful attempts were made to prepare compound (I).

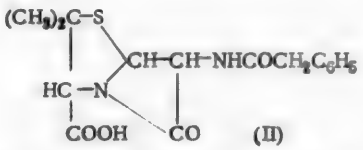
Carpenter, Turner, and du Vigneau [2] prepared benzylpenicillin by heating d-benzylpenicillic acid (III) in pyridine in the presence of pyridine hydrochloride. On this basis, the authors considered that benzyl penicillic acid was the intermediate compound in the process of formation of penicillin.



(III)



(I)



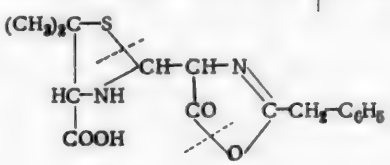
(II)

The insignificantly small yield of penicillin (0.1%) cannot serve as a conclusive argument in favor of this theory; however, at a certain step, the transformation of d-benzylpenicillic acid (III) into thiazolidine-oxazolone (I), and then into penicillin (II) must be considered. In this case the closing of the thiazolidine ring can occur by means of the reaction of the mercapto group with the ethylene-imine group of d-benzylpenicillenic acid.

The transformation of d-benzyl penicillenic acid into benzyl penicillin appears to be a two-stage process, and for this reason, it is difficult to understand the reason for the obstacle to the formation of penicillin in more significant amounts. It is possible that the above hypothesis on the course of the chemical process is incorrect.

On the other hand, the wealth of experimental material from the study of saturated and unsaturated oxazolones [3] makes possible the construction of a more or less probable hypothesis that the thiazolidine-oxazolone structure (I) must be more stable than the thiazolidine-β-lactam structure of penicillin, and that it is possible to achieve a rearrangement with the opening of the oxazolone and the closing of the β-lactam ring, as a result of the mobility of the hydrogen of the imino group of the thiazolidine group. Apparently the investigators had this hypothetical possibility in mind during attempts to solve the problem of the synthesis of penicillin.

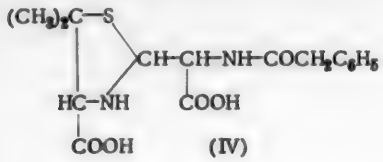
Penicillin may be looked upon as an unusually acylated thiazolidine compound with the properties of an N-acylthiazolidine-4-carboxylic acid [4]. In contrast to thiazolidine compounds, those acylated on the nitrogen atom become stable at the —S—CH— bonds (1,2-position on the thiazolidine ring). Therefore, the lability of the β-lactam ring of penicillin stabilizes its thiazolidine ring, and for this reason, penicillin is considerably more stable than its thiazolidine-oxazolone structure with two labile bonds (Ia).



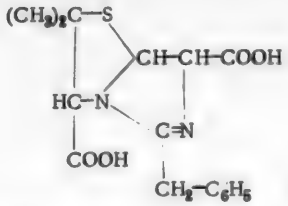
(Ia)

For this reason it is very possible that the thiazolidine-oxazolone structure, which arises, will tend to be stabilized. Because of this, as a result of the internal rearrangement, penicillin (II) can be formed; the split of the sulfur-carbon bond leads to

penicillinic acid (III), while the rupture of the carbonyl – oxygen – to penicilloinic acid (IV) or its derivatives, and finally, to penillic acid (V):



(IV)



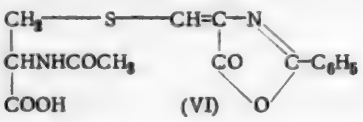
(V)

On this basis it must be considered that the thiazolidine-oxazolone structure is present at the moment of formation, and one should not search for the proof of the above theory in aimless attempts to isolate this compound. However, this view must not serve as an obstacle to attempts to synthesize penicillin by means of the thiazolidine-oxazolone structure.

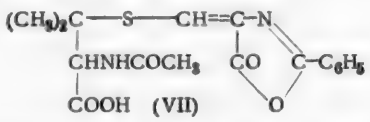
Organic chemistry, upon the study of biological reactions, enters into a new zone of its development when it encounters reactions occurring in the living organism, where newly formed structural systems rapidly change their structure; therefore, the course of chemical transformation can only be judged from the nature of the starting and final materials. All of the intermediate steps in the transformation will remain probable and unproven, as long as there are no means in the development of the processes of science for the isolation and determination of rapidly forming and disappearing structural elements in the living organism. For this reason the above hypothesis is considered satisfactory, and new proof of its probability will be sought.

It is possible that d-benzylpenicillinic acid (III) can change into the thiazolidine-oxazolone (I). For this to occur, it is necessary that the hydrogen of the mercaptan group be mobile, the ethylene-imino group be able to add to the mercaptan group, and that this be sterically possible. Attempts will be made to show these unusual conditions in model compounds.

N-Acetylcysteine has a more mobile hydrogen atom on its mercaptan group than N-acetylpenicillamine. This conclusion was made by comparing the rate of reaction of N-acetylcysteine and N-acetylpenicillamine with 4-ethoxymethylen-2-phenyl-5-oxazolone in pyridine, where it was shown that N-acetylcysteine reacts even at 0-10° while N-acetylpenicillamine reacts only at 50-55°. S-(2-phenyl-5-oxazolonylmethylen-4)-N-acetylcysteine (VI) and S-(2-phenyl-5-oxazolonylmethylen-4)-N-acetylpenicillamine (VII) are formed.



(VI)



(VII)

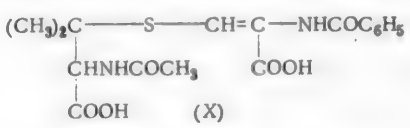
Therefore, it will be more convenient to use N-acetylcysteine for the model reactions.

If the theory on the transformation of d-benzylpenicillenic acid to the thiazolidine-oxazolone (I) is true, then, according to the known step, it must be true that N-acetylcysteine can also react with 4-aminomethylen-2-phenyl-5-oxazolone. It seemed that compound (VI) could be obtained in this manner. The reaction was effected in dry pyridine in the presence of pyridine hydrochloride in order to avoid the rupture of the oxazolone ring and bind up the ammonia that separates in the form of ammonium chloride. In spite of prolonged heating, compound (VI) could not be obtained. This may lead to the proposal that the transformation of d-benzylpenicillenic acid into thiazolidine-oxazolone is scarcely probable.

In communication (II) [5] it was shown that β-S-(α-phenyl-α-carbethoxy)-ethylenecysteine (VIII) is easily formed by the action of methoxymethylen-phenylacetic ester on cysteine in the presence of concentrated hydrochloric acid. The hydrochloric acid protects the amino group of cysteine from taking part in the closing of the thiazolidine ring. When the protection is removed, the closing of the thiazolidine ring occurs easily and the ethyl ester of (4-carboxythiazolidyl-2)-phenylacetic acid (IX) is formed:

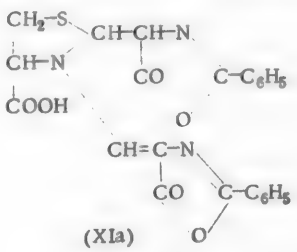
(VIII) (IX)

This reaction presented new possibilities for the preparation of [illegible] an attempt was made to prepare S-(2-phenyl-5-oxazolonylmethylen-4)-cysteine (XII) in order to then obtain the thiazolidine-oxazolone (XIII), and subsequently, desdimethylphenylpenicillin. However, compound (XII) could not be obtained by the condensation of cysteine hydrochloride with 4-ethoxymethylen-2-phenyl-5-oxazolone since a precipitate of 4-hydroxymethylen-2-phenyl-5-oxazolone formed, and the reaction did not progress any further. In such a reaction, it was found useless to remove the acetyl group of compound (VII) since the oxazolone ring ruptured first, as can be observed from the disappearance of the color, the formation of the dicarboxylic acid, and the absence of iodine-oxidizing ability in the compound. In this case the formation of α-benzoyl-β-S-(N-acetylpenicillamine)-acrylic acid (X) occurs.



(X)

The extremely great reactivity of the mercaptan and the amino groups of cysteine was used to prepare S,N-disubstituted cysteines. For example, the pyridine salt of S,N-di-(2-phenyl-5-oxazolonylmethylen-4) cysteine was formed by the condensation of cysteine hydrochloride with 4-ethoxymethylen-2-phenyl-5-oxazolone in pyridine; the free acid (XI) was then isolated. Structure (XI) was doubted for some time since a suggestion was made that the thiazolidine-oxazolone (XIII), and an unusually acylated 4-ethoxymethylen-2-phenyl-5-oxazolone (XI a) were formed in this case.



(XIa)

This doubt was removed by the study of the ultraviolet absorption spectra prepared by Yu. N. Shenker in the physico-chemical laboratory of the authors' institute. Upon the study of the spectra of S-(2-phenyl-5-oxazolonylmethylen-4)-N-acetylcysteine and S,N-di-(2-phenyl-5-oxazolonylmethylen-4')cysteine (XI), a maximum at 3600 A was obtained for the first, and two maxima, at 3600 and 3450 A, for the second; these verified the proposed structure (XI). If this compound had the structure (XIa), then the first maximum, characteristic for the mercaptomethylen-2-phenyl-5-oxazolonyl groups, would not have been found.

Upon treating S,N-di-(2-phenyl-5-oxazolonylmethylen-4)-cysteine with a 25% solution of ammonia for 5 minutes, 1 mole of 4-aminomethylen-2-phenyl-5-oxazolone precipitated quantitatively. The amide of desdimethylphenylpenicilloinic acid (XIV) was isolated in a yield of 85% of the theoretical from the mother liquor.

In order to understand how the amide of desdimethylphenylpenicilloinic acid (XIV) was formed, it was necessary to establish under what conditions does the cleavage of 4-aminomethylen-2-phenyl-5-oxazolone into compound (XI) occur. When 4-aminomethylen-2-phenyl-5-oxazolone is heated with aniline, ammonia is evolved and 4-anilinomethylenyl-phenyl-5-oxazolone is formed. Therefore the amino group can take place in exchange reactions. More characteristic was the treatment of compound (VI) with aqueous ammonia, with which 4-aminomethylen-2-phenyl-5-oxazolone could not be isolated.

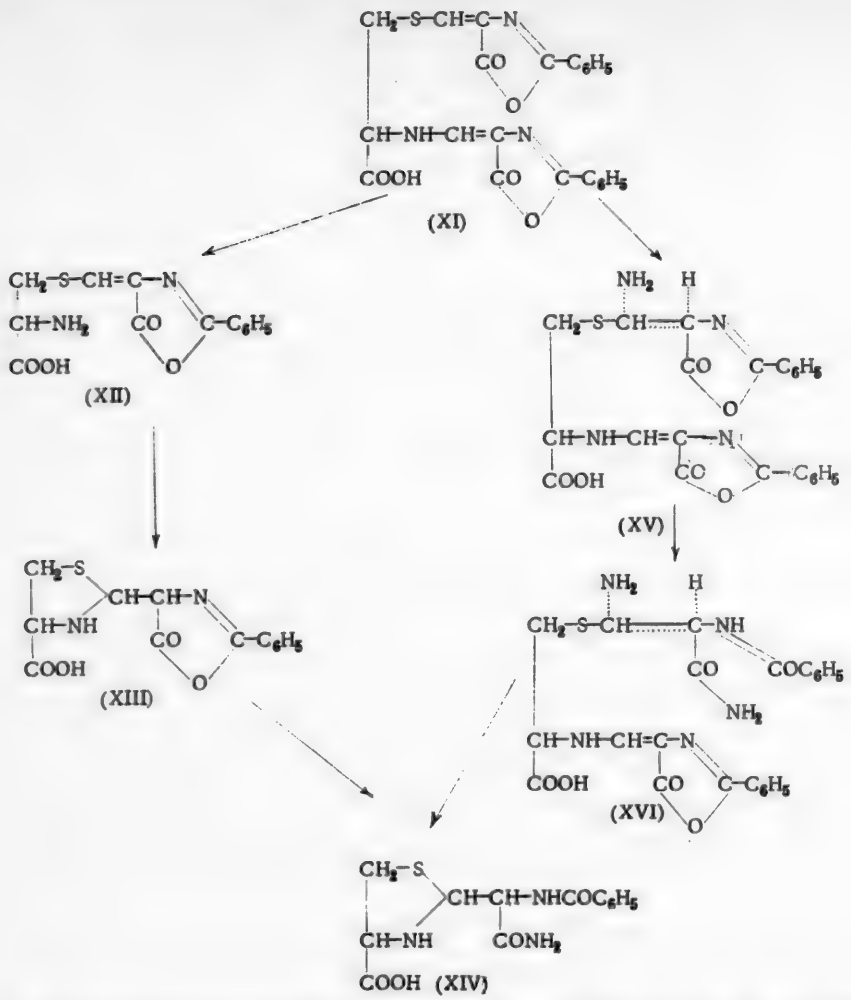
From this it could be suggested that, by the action of ammonia on compound (XI), the first intermediate compound could have been S-(2-phenyl-5-oxazolonylmethylen-4)cysteine (XII) which is transformed into the thiazolidine-oxazolone (XIII) and then, into the α-amide of desdimethylphenylpenicilloinic acid (XIV).

From the above step it is clear that another representation of the course of this reaction is: the ammonia momentarily adds to the ethylene-sulfide of compound (XI) to form the saturated oxazolone system (XV) which readily rearranges into the amide (XVI). The cleavage of 4-aminomethylen-2-phenyl-5-oxazolone and ammonia occurs simultaneously, after which the thiazolidine ring closes. It is possible that there is a somewhat different sequence of chemical transformations, but the final product of the reaction does not differ because of this.

The course of the reaction is shown in the following scheme: (see top of next page)

The structure of the α-amide of desdimethylphenylpenicilloinic acid (XIV) was determined by its synthesis from cysteine hydrochloride and diethoxymethylhippuric amide (XVII) which is readily formed by the action of aqueous-alcoholic ammonia on methyl diethoxymethylhippurate (XVII):

(XVIII) (XVII)



The amide of desdimethylphenylpenicilloinic acid (XIV) prepared by the above method, has the same melting point, does not give a depression, and crystallizes with the same crystalline system. The dinitrophenylhydrazone of formylhippuric amide was obtained from compound (XIV) upon its decomposition into cysteine and formylhippuric amide, as well as from diethoxymethylhippuric amide (XVII). Both of the dinitrophenylhydrazones formed in the above manner did not give a depression in melting point.

## EXPERIMENTAL

1-S-(2-Phenyl-5-oxazolonylmethylene-4)-N-acetylcysteine. 0.4 g of N-acetyl-l-cysteine and 0.5 g of 4-ethoxymethylene-2-phenyl-5-oxazolone were dissolved in 2 ml of dry pyridine. A crystalline precipitate began to form rapidly, and after one hour, the mass crystallized. A small amount of ether was added, the precipitate filtered, washed with ether, and then recrystallized from pyridine with ether added to cloudiness. Microcrystalline, pale yellow needles clustered into spherical crystals, m.p. 123°.

8.454 mg substance: 5.94 ml 0.01 N $H_2SO_4$ (Kjeldahl). Found %: N 9.84. $C_{15}H_{14}O_5N_2S \cdot C_5H_5N$. Calculated %: N 10.17.

The compound obtained did not contain a free mercaptan group (negative nitroprusside reaction). When the substance was treated with a 10% sodium hydroxide solution, the odor of pyridine formed.

0.2 g of the substance was treated with 1 ml of 2 N hydrochloric in the presence 100 ml of ether. The ether solution was separated, dried with sodium sulfate, and the ether removed. The residue was recrystallized from 2 ml of acetone containing 3 ml of ether. Spherical, pale yellow crystals with m.p. 166-168° (decomp.). They are soluble in hot water and acetone, and poorly soluble in ether and ethyl acetate.

8.214 mg substance: 4.80 ml 0.01 N $H_2SO_4$. Found %: N 8.18. $C_{15}H_{14}O_5N_2S$. Calculated %: N 8.38.

In contrast to thiazolidene compounds, it does not react with 0.1 N iodine solution and does not form a precipitate of 4-aminomethylen-2-phenyl-5-oxazolone on treatment with 25% ammonia solution.

S-(2-Phenyl-5-oxazolonylmethylen-4)-Nacetylpenicillamine (VII). 1.5 g of 4-ethoxymethylen-2-phenyl-5-oxazolone, 1.35 g of N-acetylpenicillamine, and 5 ml of dry pyridine were heated for 5 hours at 50-55°. The reaction mixture was transferred with 300 ml of ether to a separatory funnel, and the ether solution was treated with 10% sulfuric acid. The ether solution was washed with water, and then was shaken with 15 ml of a 5% sodium bicarbonate solution. After the separation of the ether layer, 1 liter of ether, and a 10% sulfuric acid solution were added to the water solution. The substance, which separated, dissolved in the ether, was washed with water, and dried with magnesium sulfate. After the removal of the ether, the yellow residue was recrystallized from a small amount of acetone. Pale yellow needles with m.p. 176-177° (decomp.). The substance is soluble in methyl alcohol, chloroform, dioxane, and ethyl acetate, poorly – in acetone and very poorly – in ether.

6.425 mg substance: 0.431 ml $N_2$ (20°, 730 mm). 3.990 mg substance: 0.284 ml $N_2$ (25°, 731 mm). Found %: N 7.51, 7.85. $C_{17}H_{18}O_5N_2S$. Calculated %: N 7.73.

Like compound (VI) it does not react with 0.1 N iodine solution and 25% ammonia solution.

Attempted condensation of N-acetylcysteine with 4-aminomethylen-2-phenyl-5-oxazolone. Upon heating 0.4 g of N-acetyl-l-cysteine with 0.5 g of 4-aminomethylen-2-phenyl-5-oxazolone in 6 ml of dry pyridine containing 0.2 g of hydrogen chloride for 10 hours at 50-55°, and diluting the reaction mixture with 50 ml of water, 0.48 g of 4-aminomethylen-2-phenyl-5-oxazolone with m.p. 214-215° was recovered.

α-Benzoyl-β-S-(acetylpenicillamine)-acrylic acid. 0.6 g of S-(2-phenyl-5-oxazolonylmethylen-4)-N-acetylpenicillamine was dissolved in 2 ml of concentrated hydrochloric acid. The yellow solution became colorless after 1 hour. After 6 hours the hydrochloric acid was removed in a vacuum desiccator. The residual solid, white substance was powdered and dried for a long period over sulfuric acid and sodium hydroxide in a vacuum desiccator. The substance was very soluble in water and methyl alcohol, and soluble in acetone and dioxane.

0.0955 g substance: 5.1 ml 0.1 N NaOH. Found %: COOH. 24.03. $C_{15}H_{18}O_3N_2S(COOH)_2$. Calculated %: COOH 23.68.

4-Anilinomethylen-2-phenyl-5-oxazolone. 0.7 g of 4-aminomethylen-2-phenyl-5-oxazolone, 0.4 g of aniline, and 2 ml of dry pyridine were heated for 25 hours at 80-90°; ammonia separated. The reaction mixture was added stepwise to 20 ml of 10% sulfuric acid, and a thick yellow oil separated. Yellow crystals with m.p. 154-155° were formed on treatment with methyl alcohol. They were identical with those reported in the literature [6].

S,N-Di-(2-phenyl-5-oxazolonylmethylen-4)-cysteine. 2.8 g of 4-ethoxymethylen-2-phenyl-5-oxazolone and 1 g of dl-cysteine hydrochloride were dissolved by shaking in 15 ml of dry pyridine. The yellow crystalline precipitate, which formed in a few hours, was filtered, and washed with pyridine and then with ether. It was recrystallized from pyridine and dried in a vacuum desiccator over sulfuric acid. Yellow needles with m.p. 155-156° (decomp.).

4.723 mg substance: 0.421 ml $N_2$ (23.5°, 734 mm). 0.1824 g substance: 0.0819 g $BaSO_4$. Found %: N 9.91; S 6.16. $C_{23}H_{17}O_6N_3S \cdot C_5H_5N$. Calculated %: N 10.33; S 5.91.

The pyridine salt is poorly soluble in hot water, soluble in alcohol and acetone, and insoluble in ether and benzene. When treated with 10% sodium hydroxide solution, the odor of pyridine formed.

0.5 g of the pyridine salt (XI) was shaken with 250 ml of ether in the presence of 2 ml of 2 N hydrochloric acid. The ether solution was washed with water, dried with magnesium sulfate, and the ether removed to a 20 ml volume. A yellow precipitate of spherical crystals, poorly soluble in benzene and ether, separated; m.p. 165-167° (decomp.).

5.587 mg substance: 0.451 ml $N_2$ (23°, 723 mm). 4.580 mg substance: 0.367 ml $N_2$ (23.5°, 723 mm). Found %: N 8.86, 8.78. $C_{23}H_{17}O_6N_3S$. Calculated %: N 9.07.

Decomposition of the pyridine salt (XI) with ammonia. 3 g of the pyridine salt (XI) was dissolved in 30 ml of 25% ammonia solution and left to stand for 3 hours. The precipitate, which separated, was filtered, washed with water, and dried; weight 1.087 g. After recrystallization from methyl alcohol, m.p. 215-216° (decomp.). It did not give a depression in melting point with 4-aminomethylen-2-phenyl-5-oxazolone.

The water solution was evaporated to dryness in vacuum at 40-50°, the residue was dissolved in 15 ml of water, filtered, and after cooling to 0°, acidified with 10% hydrochloric acid to a weakly acid reaction on Congo. The precipitate was filtered and washed with water; weight 1.3 g. The substance was purified by transforming it to the sodium salt and reprecipitating with hydrochloric acid. Spherical crystals with m.p. 186-187° (decomp.), soluble in warm water, and poorly soluble in most organic solvents.

4.989 mg substance: 0.592 ml $N_2$ (19.5°, 742 mm). 0.2016 g substance: 6.5 ml 0.1 N NaOH.
Found %: N 13.52; COOH 14.51. $C_{13}H_{15}O_4N_3S$. Calculated %: N 13.59; COOH 14.56.

0.2016 g of the substance in 10 ml water was titrated with 3.5 ml of 0.1 N sodium hydroxide solution to phenolphthalein, the solution acidified with a drop of hydrochloric acid, and titrated with 6.6 ml of 0.1 N iodine solution. The solution obtained readily reduced silver. A solution of diphenylhydrazine hydrochloride was added to the above solution. A microcrystalline precipitate with m.p. 207-208° (decomp.) formed. It did not give a depression in melting point with formylhippuric amide dinitrophenylhydrazone (for its preparation see below).

Diethoxymethylhippuric amide (XVII). 5 g of methyl diethoxymethylhippurate was dissolved in 30 ml of alcohol and 50 ml of 25% ammonia solution was added. The voluminous crystalline precipitate, which separated after 3 days, was filtered and recrystallized from methanol. Thin, colorless needles with m.p. 168-169°.

5.720 mg substance: 0.520 ml $N_2$ (22°, 738 mm). 6.820 mg substance: 0.617 ml $N_2$ (24.5°, 744 mm).
Found %: N 10.22, 10.18. $C_{14}H_{20}O_4N_2$. Calculated %: N 9.99.

0.9 g of the substance was dissolved in 5 ml of concentrated hydrochloric acid and left to stand for 1 hour at 0°; 1 ml of the solution was diluted with 10 ml of water, and a solution of dinitrophenyl hydrazine hydrochloride was added. A microcrystalline precipitate of formylhippuric amide phenylhydrazone with m.p. 208-209° (decomp) separated.

Amide of desdimethylphenylpenicilloinic acid (XIV). 0.5 g dl-cysteine hydrochloride, 0.8 g of diethoxymethylhippuric amide were heated for 5 hours at 70° in 15 ml of 50% ethyl alcohol; a test for the mercaptan group by means of nitroprusside reaction almost completely disappeared. The next day the precipitate was filtered and purified by reprecipitating a solution of the ammonium salt with hydrochloric acid. White, spherical crystals with m.p. 186° (decomp).,

4.515 mg substance: 0.537 ml $N_2$ (21.5°, 746 mm). 4.900 mg substance: 0.593 ml $N_2$ (21°, 740 mm).
Found %: N 13.57, 13.78. $C_{13}H_{15}O_4N_3S$. Calculated %: N 13.59.

## SUMMARY

It was shown that 4-aminomethylen-2-benzyl-5-oxazolone and the α-amide of desdimethylphenylpenicilloinic acid were formed by the action of aqueous ammonia on S,N-di-(2-phenyl-5-oxazolonylmethylen-4)-cysteine.

A suggestion was made that the reactions forming the α-amide of desdimethylphenylpenicilloinic acids occur with S-(2-phenyl-5-oxazolonylmethylen-4)-cysteine and 2'-(2-phenyl-5-oxazolonyl-4)-thiazolidine-4-carboxylic acid as intermediate compounds.

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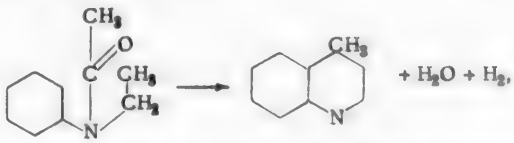
• See Consultants Bureau English translation, p. 1077.

# DERIVATIVES OF QUINOLINE

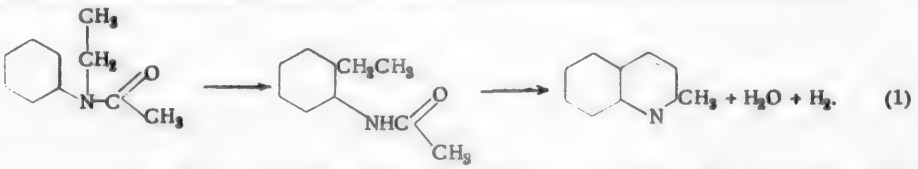
## IX. ON THE MECHANISM OF THE PICTET REACTION

B. I. Ardashev and B. A. Tertov

Attempts to cyclize various organic compounds of apparently similar structure into γ-quinoline derivatives often lead to α-substituted ones. Several examples are: The anils of crotonaldehyde and cinnamaldehyde, upon distillation in the presence of mineral acids, form quinaldine [1], and α-phenylquinoline [2] respectively; lack of knowledge of the above was the reason for the incorrect interpretation of the mechanism of the quinaldine synthesis [3]. Pictet and Barbier attempted to synthesize γ-phenylquinoline from formanilide and acetophenone, but obtained α-phenylquinoline as a result [4]. Pictet and Bunzl effected the condensation of ethyl acetanilide expecting to obtain lepidine according to the scheme:



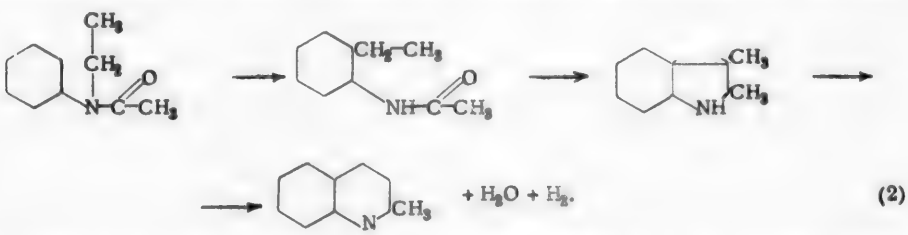
but obtained quinaldine; according to them, the mechanism of the reaction was as follows [5] (1):



(1)

o-Ethylacetanilide was found, by the authors, to be the intermediate product. However, acetylmethylaniline formed quinoline under these conditions [6]; the mechanism of the reaction in this case must be different. Pictet and Fert isolated o-acetyltoluidine from the reaction mixture [6]. They proposed that the reaction occurs by means of the intermediate formation of the methyl ketol (α-methylindole) because E. Fischer observed that the methyl ketol was transformed into quinoline upon heating in the presence of zinc chloride [7].

The synthesis of quinaldine from ethylacetanilide, by analogy, can be explained by the scheme (2):

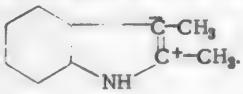


(2)

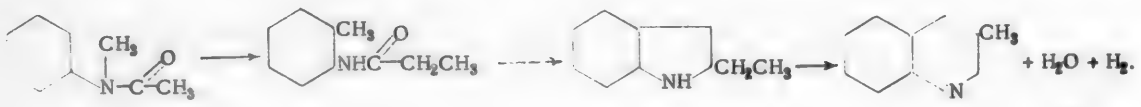
If the rupture of the indole ring occurs at the double bond between the α- and β-carbon atoms, which is more likely and is supported by the expansion of the pyrrole ring into the pyridine ring [8], then, in relation to which of the two methyl groups enters into the formation of the pyridine ring, either lepidine (case where the α-methyl group participates) or quinaldine can be formed. The formation of lepidine by means of this reaction can be of practical interest, as it is known that, when the ketol is passed through a weakly red hot tube, up to 17% of quinoline is formed [9].

In the present investigation it was shown that 2,3-dimethylindole formed quinaldine upon heating with zinc chloride, which confirms scheme (2). On the basis of the alternating polarity and the orientation effect,

it can be suggested that the methyl group in the β-position will participate more readily in the formation of the pyridine ring than the methyl group in the α-position because the negative charge on the carbon atom of the α-methyl group is strengthened by the polarizing effect from the site of the NH-group, stabilizing its bond with the positive α-carbon atom of the ring, whereas the negative charge on the carbon atom of the β-methyl group is weakened by the effect of the NH-group which also affects the character of the charge on the β-carbon atom of the ring; thus the bond of the methyl group with the β-carbon atom must be more labile.



In the case of methylpropionylaniline or o-propionyltoluidine, β-methylquinoline is formed upon heating with zinc chloride; the reaction occurs by means of the intermediate formation of α-ethylindole according to scheme (3):



(3)

From the mechanism proposed by the authors for the Pictet reaction it can be concluded that it is impossible to obtain lepidine, as Pictet desired, by means of the reaction because the various homologs of indole formed are transformed into α- and β-substituted quinolines by the rupture of the ring. The only structure of indole which can explain the formation of lepidine is, apparently, the indolenyl:

The formation of quinoline derivatives by fusing homologs of indole with zinc chloride can be used for the identification of the various indole homologs which usually form picrates poorly or not at all whereas quinolines do so readily.

## EXPERIMENTAL

The starting materials were the acylated derivatives of methylaniline, ethylaniline, and o-toluidine which had melting points corresponding to those given in the literature. o-Propionyltoluidine was obtained by the action of propionic acid on the amine [10]. Methylated acetyl and propionyl anilines were obtained by the action of metallic sodium and methyl iodide on the corresponding acyl derivatives [11]. The yields of the quinoline derivatives were small and, as a rule, did not exceed 0.5-0.7 g. The crude bases were identified by means of their picrates or styphnates which were obtained in pure form by recrystallization from alcohol to a constant melting point.

Synthesis of quinoline. Experiment 1. A mixture of 15 g of methylacetanilide and 15 g of zinc chloride was heated in an oil bath for 6 hours at 290-300°. Upon cooling, the melt was dissolved in hydrochloric acid, was made alkaline with 40% sodium hydroxide, and the bases were steam distilled. The distillate was extracted with ether, the ether extract was dried with solid potassium hydroxide, and the ether was removed. The crude bases were boiled for 15 minutes with 5 ml of acetic anhydride. Upon cooling, the mixture was made alkaline with saturated sodium carbonate solution, the quinoline was steam distilled, and extracted with ether. The picrate of the base had the m.p. 198° after three recrystallizations from alcohol. No depression was given upon a mixed melting point determination with quinoline picrate.

Experiment 2. A mixture of 15 g of acet-o-toluidine and 15 g of zinc chloride was heated in an oil bath for 6 hours at 290-300°. The separation and the purification of the bases was effected as in the first experiment. The picrate of the base isolated had the m.p. 200° after 3 recrystallizations. No depression was obtained on mixed melting point determination with quinoline picrate.

0.1 g substance: 14.2 ml $N_2$ (23°, 756 mm). Found %: N 15.83. $C_9H_7N \cdot C_6H_2(NO_2)_3OH$. Calculated %: N 15.64.

Experiment 3. 15 ml of phenylhydrazine and 15 ml of acetone were heated for one hour at 100°. The resulting acetone phenylhydrazone was heated with 25 g of zinc chloride for 3 hours at 290-300°. The isolated

bases were processed in an analogous manner to the previous experiments. The picrate obtained from the isolated oil had the m.p. 200° after 4 recrystallizations from alcohol. No depression was obtained upon a mixed melting point determination with quinoline picrate.

Synthesis of quinaldine. Experiment 4. A mixture of 15 g of ethylacetanilide and 15 g of zinc chloride was heated for 4 hours in an oil bath to 260-270°. The isolation of the picrate of the base was effected as reported above. No depression was obtained upon a mixed melting point determination with quinaldine picrate. The styphnate of the base had the m.p. 211°.

Experiment 5. 15 ml of phenylhydrazine, 20 ml of methyl ethyl ketone, and 25 g of zinc chloride were used. The experiment was conducted analogously to the third experiment. The picrate of the base isolated had the m.p. 190°. No depression was obtained upon a mixed melting point determination with quinaldine picrate. The styphnate of the base had the m.p. 212°.

0.1145 g substance: 15.6 ml $N_2$ (22°, 754 mm). Found %: N 15.23. $C_{10}H_9N \cdot C_6H_2(NO_2)_3OH$. Calculated %: N 15.05.

Synthesis of 3-methylquinoline. A picrate of a base with m.p. 186°, giving a depression upon a mixed melting point determination with quinaldine picrate was isolated upon the reaction of methylpropionylaniline with zinc chloride in a manner analogous to the above experiment. The styphnate of the base had the m.p. 185° which corresponds to β-methylquinoline.

## SUMMARY

1. It was shown that the α- and β-substituted quinolines were formed upon heating alkylated acetanilides and acylated o-toluidines with zinc chloride.

2. A general mechanism was proposed for the formation of quinoline derivatives from alkylated acyl anilides by the Pictet reaction.

3. On the basis of the proposed mechanism for the Pictet reaction it can be concluded that γ-alkyl quinolines cannot be obtained by means of this reaction.

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[9] A. Pictet, Ber., 38, 1947 (1905).

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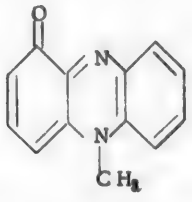
• See Consultants Bureau English translation, p. 493.

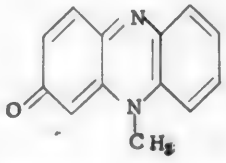
# N-ALKYLPHENAZINONES. I

S. B. Serebryanyi

N-Alkylphenazinones have been little studied in spite of the fact that this group includes the antibiotic of B. pyocyaneus – pyocyanine. The preparation of a small amount of N-alkylphenazinones has been reported in the literature [1-5]. The simplest N-alkylphenazinones were obtained by the oxidation of aqueous solutions of quaternary phenazine salts. It was shown [2] that, in relation to the method of oxidation of phenazine methylmethosulfates, isomeric N-alkylphenazinones were obtained: photochemical oxidation leads to the formation of blue 10-methylphenazinone-1 (pyocyanine), while oxidation of the same salt with potassium permanganate in alkaline media results in the formation of the red 10-methylphenazinone-3.



10-Methylphenazinone-1
(blue)

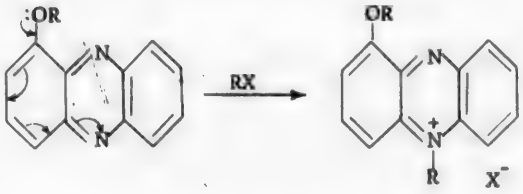


10-Methylphenazinone-3
(red)

The same picture is obtained upon the oxidation of phenazine ethylethosulfate.

The author, having a series of alkoxy derivatives of phenazine [6-9] at his disposal, prepared a series of new alkoxy derivatives of 10-ethylphenazine by the oxidation of aqueous solutions of their quaternary salts with potassium permanganate in alkaline media.

Several (more than two) isomeric N-alkylphenazinones can be formed upon the oxidation of quaternary salts of substituted phenazines; for example, 1-alkoxyphenazines. The structure of these N-alkylphenazinones must depend on the structure of the quaternary salts, To answer the question of the possible structures of the quaternary phenazine salts, the electronic character and the direction of the influence of the substituent must be considered. Alkoxy- and hydroxy groups belong to the series of electropositive substituents. When found in position 1 or 3 of the benzene ring of phenazine, these groups, as a result of the displacement of the electrons, cause an increase in the electron density of one of the nitrogen atoms of this heterocycle, and, apparently upon the formation of salts, the proton or alkyl will add only to this nitrogen atom.



Experimentally it was shown that the structure of the quaternary 1-hydroxy- and 1-methoxyphenazine salts agreed only with these rules. For example, in 1938, Hillemann [10] showed that, upon the action of dimethyl sulfate on 1-methoxyphenazine, the methyl group added to the nitrogen atom in position 10.

It was shown that, upon the desalkylation of 1-methoxyphenazine ethylethosulfate with 60% sulfuric acid, blue 10-ethylphenazinone-1 was formed. Therefore, the alkyl group in the quaternary salt of 1-alkoxyphenazine is also found on the nitrogen in position 10. In the case of two hydroxy or alkoxy groups, the direction of their effect may be concurrent or opposed. In the latter case, two isomeric salts must be expected.

TABLE 1

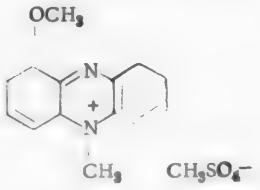
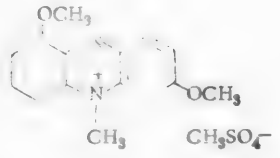
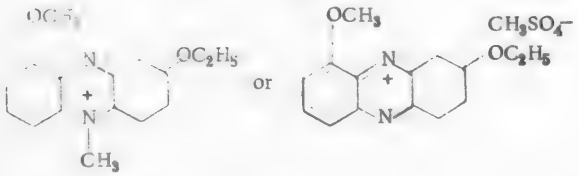
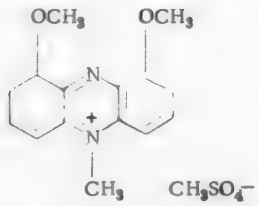
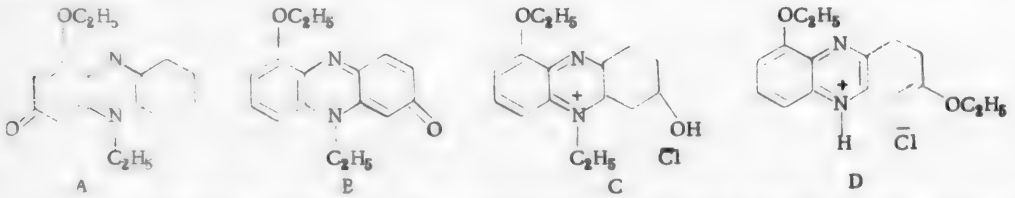
| Expt. No. | Structure of salts | Melting point | Appearance |
|---|---|---|---|
| I |  | 201°• | Dark, red needles |
| II |  | Does not melt up to 300° | Red needles |
| III |  | 197°• | Red needles |
| IV |  | Does not melt up to 300° | Violet needles |

Table 1 lists the structures, melting points, and the external appearance of the alkoxyphenazine methylmethosulfates obtained by the action of dimethyl sulfate on the corresponding bases. The structure of the quaternary salts (I) was shown experimentally, the structure of the remaining salts was suggested on the basis of the above given rule.

It must be pointed out that, upon the alkylation of 1-methoxy-7-ethoxyphenazine, only one salt was isolated instead of the two possible: the structure of the salt, (III), is listed in Table 1. The alkoxyphenazine methylmethosulfates obtained are readily soluble in water and alcohol in the cold; they could be purified by several recrystallizations from a mixture of alcohol and amylacetate, whereupon they all crystallized with one molecule of water.



A B C D

Aqueous solutions of salts (I), (II), and (IV) are completely stable on prolonged storage, while the aqueous solution of salt (III) hydrolyzes on standing with the separation of the free base.

Upon oxidation of 1-ethoxyphenazine ethylethosulfate, the formation of three isomeric 10-ethyl-

• Melts with decomposition. The temperature here and subsequently is given without correction.

phenazinones could be expected: 2 red (1-ethoxy-10-phenazinone-3 and 1-ethoxy-10-ethylphenazinone-6) and one blue (1-ethoxy-10-ethylphenazinone-8). It was found that alkoxy- and dialkoxyphenazinone ethylethosulfates cannot be oxidized photochemically. In contrast, the oxidation of these salts with potassium permanganate in alkaline media proceeds readily and smoothly, and leads to the formation of red 10-ethylphenazinones which, apparently, are derivatives of 10-ethylphenazinone-3 or 10-ethylphenazinone-6.

In one case, when 1-ethoxyphenazine ethylethosulfate was oxidized, two red isomers of 1-ethoxy-10-ethylphenazinone were obtained: with m.p. 211-212° and 195-197°, the structures of which can be represented by the formulas A and B.

The preparation with m.p. 211-212° dissolves in dilute hydrochloric acid with a red color, while the preparation with m.p. 195-197° – with a yellow color. The color of the hydrochloric acid solution of the latter substance is the same as that of 1,6-diethoxyphenazine, D. Apparently when 1-ethoxy-10-ethylphenazinone is dissolved in hydrochloric acid, hydroxyethoxyethylphenazine chloride, C, is formed.

The closeness of the colors of the hydrochloric acid solutions of 1-ethoxy-10-ethylphenazinone with m.p. 195-197° and 1,6-diethoxyphenazine, leads to the conclusion that the phenazinone is 1-ethoxy-10-ethylphenazinone-6, and therefore, its isomer with m.p. 211-212° is 1-ethoxy-10-ethylphenazinone-3.

Upon oxidation of the dialkoxyphenazine ethylethosulfates, only one red 10-ethylphenazinone was obtained. 10-Ethyldialkoxyphenazinones are derivatives of either, 10-ethylphenazinone-3, or 10-ethylphenazinone-6; whereas preparation (X) can only have one structure (Table 2).

Table 2 contains the structures, melting points, and the yields of the red 10-ethylphenazinones obtained.

The red N-alkylphenazinones are readily soluble in alcohol and chloroform, and insoluble in ether, petroleum ether, and ligroin. They are noticeably soluble in cold water and readily soluble in hot water. Upon dissolving 10-ethylphenazinones in aqueous alkali solutions, the color remains unchanged from that in the aqueous solution. Dilute mineral acids dissolve 10-ethylphenazinones in the cold, whereupon the color of the acidic solution differs from the color of the aqueous solution, which is related to the formation of the hydrochloride salt of the alkoxy derivatives of 2-hydroxyphenazine (see above).

## EXPERIMENTAL

### Alkoxyphenazine ethylmethosulfates.

Alkoxyphenazine methylmethosulfates were prepared by heating alkoxyphenazines with an excess of freshly distilled dimethyl sulfate in nitrobenzene in a sealed tube for 5-15 min. on a boiling water bath. The reaction product was treated with dry ether and filtered. In order to separate the unreacted bases, the nitrobenzene, and the excess dimethyl sulfate, the salt obtained was treated with boiling petroleum ether. The methylmethosulfates were purified by five recrystallizations from a mixture of alcohol and amyl acetate. After four recrystallizations, the melting point did not change.

1-Methoxyphenazine methylmethosulfate (I). 0.7 g of the crude salt was obtained by heating 0.5 g of the base with 0.8 ml of dimethyl sulfate in 5 ml of nitrobenzene for 5 min. 0.2 g of the pure salt was obtained after recrystallization.

Found %: N 8.14, 8.16. $C_{15}H_{16}O_5N_2S \cdot H_2O$. Calculated %: N 7.92.

1,6-Dimethoxyphenazine methylmethosulfate (II). 0.39 g of the impure salt from which, 0.15 g of the pure salt was obtained, was prepared by heating 0.4 g of the base and 0.4 g of dimethyl sulfate in 2 ml of nitrobenzene for 5 min.

Found %: N 7.34. $C_{16}H_{18}O_6N_2S \cdot H_2O$. Calculated %: N 7.30.

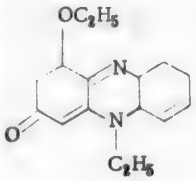
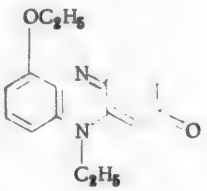
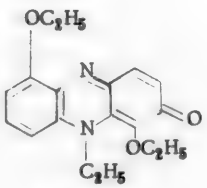
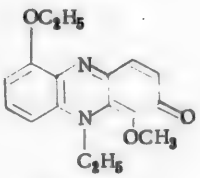
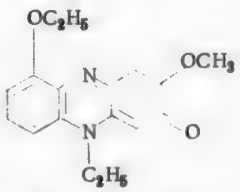
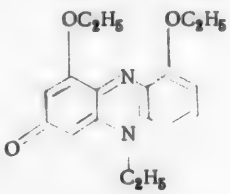
1-Methoxy-7-ethoxyphenazine methylmethosulfate (III). A mixture of 0.5 g of the base, 0.8 ml of dimethyl sulfate, and 2.5 ml of nitrobenzene was heated for 15 min. 0.8 g of the impure salt was obtained; after purification, 0.1 g. The salt dissolved in water with an orange yellow color. The aqueous salt solution, upon standing for 24 hours, hydrolyzed with the separation of the free base.

Found %: N 7.02, 6.98. $C_{17}H_{20}O_6N_2S \cdot H_2O$. Calculated %: N 7.05.

1,8-Dimethoxyphenazine methylmethosulfate (IV). The quaternary salt, in amount 0.67 g, was obtained by heating 0.5 g of the base, and 0.8 ml of dimethyl sulfate in 2.5 ml of nitrobenzene for 10 min. 0.2 g of the pure salt was obtained. Long, dark, violet needles. The aqueous solution was colored dark red.

Found %: N 7.04, 7.02. $C_{16}H_{18}O_6N_2S \cdot H_2O$. Calculated %: N 7.30.

TABLE 2

| Expt. No. | Name of preparation | Formula | Melting point | Yield from the base, in % |
|---|---|---|---|---|
| V | 1-Ethoxy-10-ethylphenazinone-3 |  | 211-212° | 90 |
| VI | 1-Ethoxy-10-ethylphenazinone-6 |  | 195-197 | |
| VII | 1,5-Diethoxy-10-ethylphenazinone-6 |  | 205 | 69 |
| VIII | 1-Ethoxy-5-methoxy-10-ethylphenazinone-6 |  | 225-226 | 44 |
| IX | 1-Ethoxy-7-methoxy-10-ethylphenazinone-6 |  | 185-186 | 46 |
| X | 1,8-Diethoxy-10-ethylphenazinone-3 |  | 211-212° | 52 |

## 10-Ethylphenazinones

10-Ethylphenazinone-1. This phenazinone was prepared by the desalkylation of 1-methoxyphenazine ethylethosulfate. The quaternary salt was obtained from 0.35 g of the base in the same manner as 1-ethoxyphenazine ethylethosulfate (see below). 0.4 g of a pure preparation was obtained by treating the impure quaternary salt with ether. The salt obtained was dissolved in 10 ml of 60% sulfuric acid, the solution heated on an oil bath to

175°, and kept at this temperature for 3 min., and then poured into water. The dilute sulfuric acid solution was filtered and made alkaline with a 5% sodium hydroxide solution. The color of the solution changed from red to blue. The alkaline solution was extracted with chloroform, and the chloroform solution was extracted with small amounts of 5% hydrochloric acid. The acidic solution was made alkaline and once more extracted with chloroform. 0.1 g of crystalline 10-ethylphenazinone-1 was obtained after the removal of the solvent. Blue needles with m.p. 170-173° were obtained on recrystallization from water.

Derivatives of 10-ethylphenazinone-3 and 10-ethylphenazinone-6 (red phenazinones). These compounds were obtained by the oxidation of ethoxy substituted phenazine ethylethosulfates. The ethylethosulfates were obtained by heating the bases with excess neutral diethyl sulfate and nitrobenzene. The heating was conducted on an oil bath at 130-140° for 1-2 hours. The salts obtained were treated with small quantities of water, the aqueous solution was extracted with benzene to remove the nitrobenzene and excess diethyl sulfate, and the unreacted base, and then the aqueous solution was filtered. Potassium permanganate was dissolved in the aqueous solution of the quaternary salt, and a small excess of 10% sodium hydroxide solution was added dropwise with mechanical stirring in 45 min. The phenazinone, which formed on standing over night, was extracted with chloroform, the solvent removed, and the preparation purified by crystallization from water or from a mixture of ligroin and dioxane.

On treating the benzene solution with 15% hydrochloric acid followed by precipitation with ammonia, phenazine bases which did not react during the preparation of the ethylethosulfates were regenerated.

1-Ethoxy-10-ethylphenanzinone-3 and 1-ethoxy-10-ethylphenazinone-6 (V and VI). The ethylethosulfate was obtained by heating 1 g of 1-ethoxyphenazine and 3 ml of diethyl sulfate in 5 ml of nitrobenzene for 50 min. In order to oxidize it, 3.4 g of potassium permanganate and 9 ml of 10% sodium hydroxide were added to the solution of the salt in 60 ml of water. 0.75 g of a red substance with m.p. 191-205°, was obtained. The substance was shown to be a mixture of two isomeric red phenazinones. 0.3 g of an isomer with m.p. of 208-211° was isolated from the mixture after recrystallization from water. It was recrystallized from water for analysis. Dark, red needles, m.p. 211-212°.

Found %: N 10.49. $C_{16}H_{16}O_2N_2$. Calculated %: N 10.44.

The substance dissolved in dilute hydrochloric acid with a red color. The aqueous mother liquor from the isolation of the isomer with m.p. 208-211° was extracted with chloroform. After removal of the chloroform, the solid residue was recrystallized from a mixture of ligroin and dioxane. 0.3 g of red needles of 1-ethoxy-10-ethylphenazinone-6 with m.p. 195-197° was isolated. For analysis the preparation was recrystallized from the above mixture; the melting point did not change.

Found %: N 10.25, 10.60. $C_{16}H_{16}O_2N_2$. Calculated %: N 10.44.

A mixed melting point determination with the isomeric phenazinone (V) gave a 15-20° depression. 1-Ethoxy-10-ethylphenazinone-6 is readily soluble in cold water. Its hydrochloric acid solution is colored yellow.

1,5-Diethoxy-10-ethylphenazinone-6 (VII). The ethylethosulfate was obtained by heating 1 g of the base with 3 ml of diethyl sulfate and 3 ml of nitrobenzene for 2 hours. The processing of the salt and its oxidation was effected as previously. The yield of the impure preparation was 0.6 g. For analysis, the preparation was recrystallized three times from hot water. Long, thread-like, violet needles, m.p. 205°.

Found %: N 8.96, 8.78. $C_{18}H_{20}O_3N_2$. Calculated %: N 8.94.

1-Ethoxy-5-methoxy-10-ethylphenazinone-6 (VIII). The ethylethosulfate was obtained from 0.2 g of the base with the same method as in the previous case; the same oxidation method was used. The yield of the substance with m.p. 223-225° was 0.1 g. For analysis, the substance was recrystallized two times from hot water. Violet needles, m.p. 225-226°.

Found %: N 9.42. $C_{17}H_{18}O_3N_2$. Calculated %: N 9.39.

1-Ethoxy-7-methoxy-10-ethylphenazinone-6. A solution of 1 g of the base and 2 ml of diethyl sulfate in 3 ml of nitrobenzene was heated for 1hour and 15 min. 4 g of potassium permanganate and 10 ml of 10% sodium hydroxide solution were added to a solution of the salt in 50 ml of water. 0.39 g of a substance with m.p. 183-185° was obtained. For analysis, it was recrystallized from water. Dark red needles, m.p. 185-186°.

Found %: N 9.29, 9.43. $C_{17}H_{18}O_3N_2$. Calculated %: N 9.39.

1,8-Diethoxy-10-ethylphenazinone-3 (X). The quaternary salt was prepared by heating 0.5 g of 1,8-diethoxyphenazine and 0.7 ml of diethyl sulfate in 1 ml of nitrobenzene for 1 hour. A solution of the salt in 45 ml of water was oxidized with 1.3 g of potassium permanganate with the addition of 5 ml of a 10% sodium hydroxide solution 0.24 g of dark red crystals with m.p. 206-208° was obtained. For analysis, the preparation was recrystallized from a mixture of dioxane and ligroin.

Dark red needles, m.p. 211-212°.

Found %: N 8.83. $C_{18}H_{20}O_3N_2$. Calculated %: N 8.94.

The author wishes to express his gratitude to Academician of the Academy of Sciences of the Ukranian S.S.R., prof. A.I. Kiprianov, for valuable suggestions during this investigation

## SUMMARY

1. The following methylmethosulfates were obtained: 1-methoxy-, 1,6-dimethoxy-, 1,8-dimethoxyphenazines, and 1-ethoxy-7-methoxyphenazine.

2. 10-Ethylphenazinone-1 was formed upon the desalkylation of 1-methoxyphenazine ethylethosulfate; this operation determined the structure of the above salt.

3. It was shown that quaternary alkoxyphenazine salts were not oxidized photochemically.

4. Five new derivatives of 10-ethylphenazinone-3 and one of 10-ethylphenazinone-6 were obtained by the oxidation of aqueous solutionsof alkoxyphenazine ethylethosulfates with potassium permanganate in alkaline media.

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# CYANINE DYES CONTAINING FLUORINE

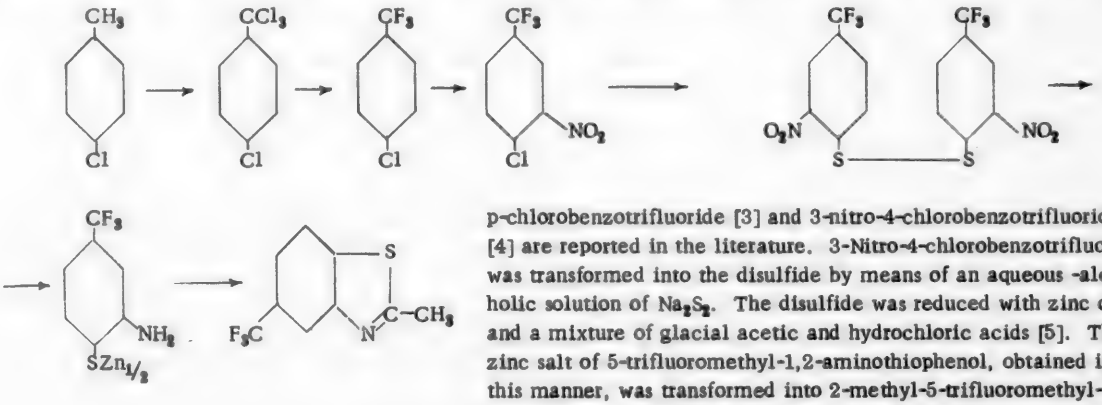
## II. CYANINE DYES FROM DERIVATIVES OF 6-FLUORO- AND 5-TRIFLUOROMETHYLBENZOTHIAZOLES

A. I. Kiprianov and L. M. Yagupolsky

In the previous communication [1] the preparation of a series of cyanine dyes from derivatives of 6-fluorobenzothiazole were reported. In the present communication, the synthesis of dyes containing a fluorine atom and a $CF_3$- group in the 5,5'- positions of the benzothiazole ring are given.

In the literature mostly in patents, are reported anthraquinone, indigoid, and azo dyes with a trifluoromethyl group as a substituent. Several of these have been prepared on an industrial scale. Up to now, the least studied were the trifluoromethyl derivatives of the cyanine dyes. Only one patent reporting asymmetrical trimethinecyanines, containing a $CF_3$- group in the benzimidazole ring has been published [2]. The absorption maxima of these dyes are not given in the patent, and for this reason, no conclusion on the effect of the $CF_3$- group on the color can be made.

In order to prepare thiacyanine dyes containing a $CF_3$-group, 2-methyl-5-trifluoromethylbenzthiazole, unreported in the literature, was synthesized for use as the starting material according to the following scheme:



p-chlorobenzotrifluoride [3] and 3-nitro-4-chlorobenzotrifluoride [4] are reported in the literature. 3-Nitro-4-chlorobenzotrifluoride was transformed into the disulfide by means of an aqueous -alcoholic solution of $Na_2S_2$. The disulfide was reduced with zinc dust and a mixture of glacial acetic and hydrochloric acids [5]. The zinc salt of 5-trifluoromethyl-1,2-aminothiophenol, obtained in this manner, was transformed into 2-methyl-5-trifluoromethylbenzthiazole by boiling with acetic anhydride.

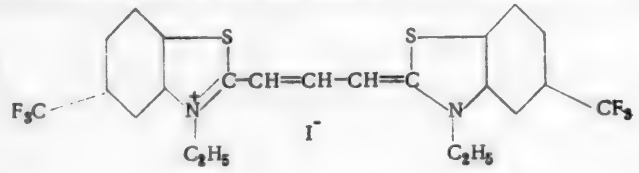
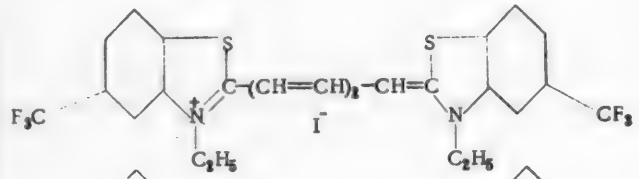
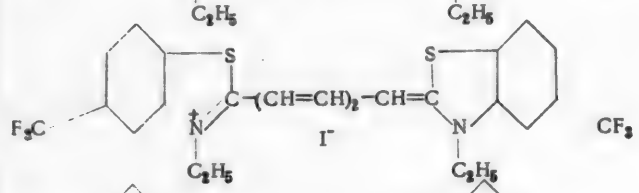
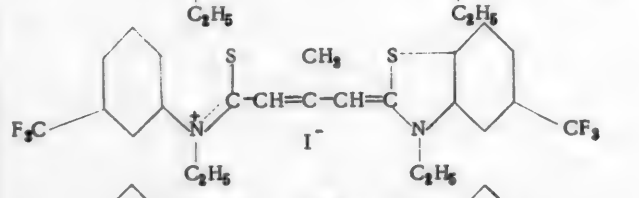
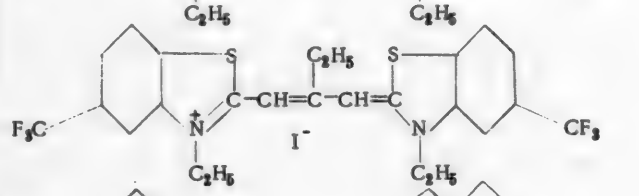
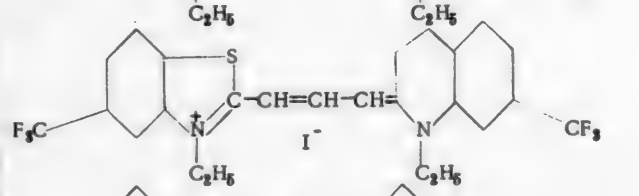
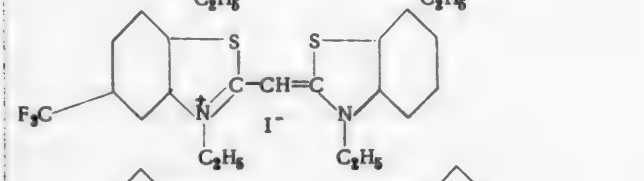
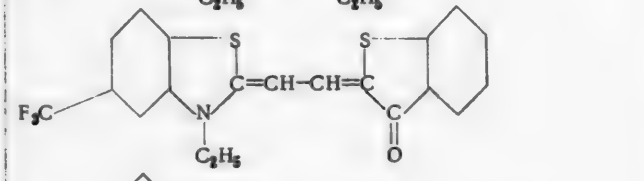
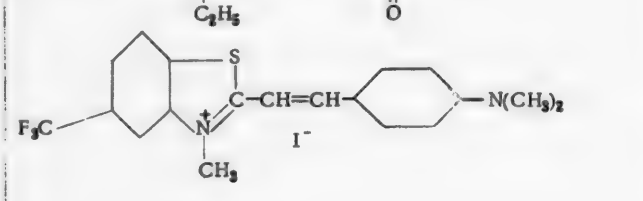
The structure of the 2-methyl-5-trifluoromethylbenzthiazole was determined by its transformation into 2-methylbenzthiazole-5-carboxylic acid by the hydrolysis of the trifluoromethyl group upon heating with sulfuric acid. Since this acid was not reported in the literature, it was synthesized from 2-methyl-5-aminobenzthiazole via 2-methyl-5-cyanobenzthiazole. The acids obtained by the two methods both melted at 202-203°. No depression was given upon a mixed melting point determination.

The methiodide and ethiodide were obtained from 2-methyl-5-trifluoromethylbenzthiazole, and from these were obtained 9 thiacyanines with a trifluoromethyl group, specifically: symmetrical and asymetrical trimethinecyanines, penta- and heptamethinecyanines, asymmetrical monomethinecyanines, as well as merocyanine and the dye- styryl. The structural formulas and the absorption maxima of these preparations in ethyl alcohol are listed in Table 1; for comparison, the absorption maxima of the corresponding dyes lacking the trifluoromethyl group are also given. From Table 1, it is apparent that the absorption maxima of 5,5'- bis-(trifluoromethylthiacarbocyanine) does not differ from those of the unsubstituted dyes. It is interesting to compare the effect of the trifluoromethyl group on the color of thiacarbocyanines with that of the nitro group, which resembles it in electronegative properties. E.D.Sych [6] synthesized 5,5'-dinitrothiacarbocyanines, differing very little in absorption maximum (560 mμ) from the unsubstituted dyes.

The thiacyanines with trifluoromethyl groups are somewhat more stable to the action of light than the corresponding unsubstituted dyes.

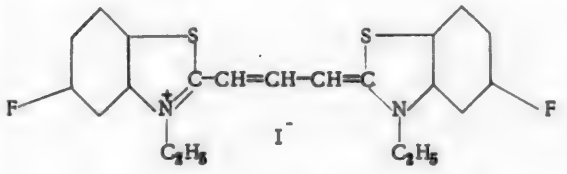
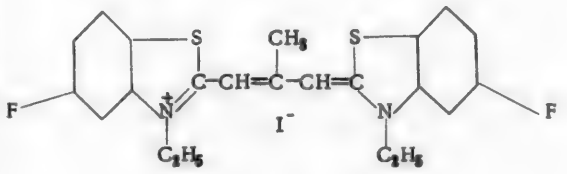
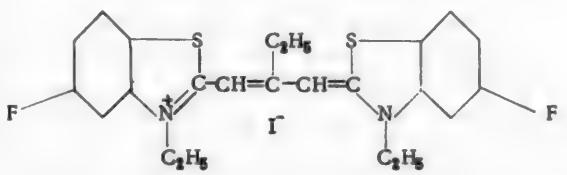
For the synthesis of 5,5'dinitrothiocarbocyanines, it was necessary to obtain 2-methyl-5-fluorobenthiazole

TABLE 1

| Expt. No. | Formula | λ max (in mμ) | λ max of dye without $CF_3$-group |
|---|---|---|---|
| I |  | 557 | 558 |
| II |  | 651 | 651 |
| III |  | – | 755 |
| IV |  | 544 | 544 |
| V |  | 550 | 550 |
| VI |  | 570 | 580 |
| VII |  | 425 | 422 |
| VIII |  | 545 | 556 |
| IX |  | 540 | 530 |

unreported in the literature – as the starting material. It was obtained from 2-methyl-5-aminobenzthiazole by diazotizing with sodium nitrite in a solution of fluoboric acid. The precipitated fluoborate diazonium compound was decomposed by heating in decalin. The ethiodide of this base was obtained, and from it, three thiacarbocyanines with fluorine atoms in the 5,5'-positions were obtained (Table 2).

TABLE 2

| Expt. No. | Formula | $\lambda_{max}$ in mμ | $\lambda_{max}$ of dye without fluorine |
|---|---|---|---|
| X |  | 562 | 558 |
| XI |  | 546 | 545 |
| XII |  | 550 | 550 |

Fluorine and chlorine, present as substituents in 5,5'-positions, displace the absorption maxima of thiacarbocyanines somewhat more than when they are present in position 6,6'. This is apparent from Table 3.

TABLE 3

| Substituent | Position of substituent | $\lambda_{max}$ (in mμ) | Position of substituent | $\lambda_{max}$ (in mμ) |
|---|---|---|---|---|
| – | – | 558 | – | 558 |
| Fluoro | 5 | 562 | 6 | 558 [1] |
| Chloro | 5 | 562.5 [7] | 6 | 560 [8] |

## EXPERIMENTAL

### Intermediate product

4,4'-Bis(trifluoromethyl)-2,2'-dinitrodiphenyldisulfide. 4 g of $Na_2S \cdot 9H_2O$ was dissolved in 35 ml of alcohol in a 100 ml round bottomed flask connected with a reflux condenser. 0.53 g of finely pulverized sulfur was added to the solution and the liquid heated for 1 hour until the sulfur dissolved. The hot solution was added in small portions to a boiling solution of 7.2 g of 3-nitro-4-chlorobenzotrifluoride in 10 ml of alcohol. When all of the disulfide was added, the mixture was heated on the water bath for 3 hours. After cooling, the mixture of disulfide and sodium chloride was heated and washed with water. After recrystallization from alcohol, the product was obtained in the form of long yellow needles with m.p. 161-162°. Yield 5 g or 70% of the theoretical.

Found %: N 6.45, 6.52. $C_{14}H_6O_4N_2S_2F_6$. Calculated %: N 6.30.

2-Methyl-5-trifluoromethylbenzthiazole. 10.5 g of 4,4'-bistrifluoromethyl-2,2'-dinitrodiphenyldisulfide was dissolved by heating in 65 ml of glacial acetic acid. 18 g of zinc dust and 45 ml of concentrated hydrochloric acid was added to the solution in small portions. The reduction took 1 hour. At the end of the reaction, the yellow solution became colorless. The solution was filtered, diluted, with 3-fold quantity of water, sodium acetate added until the absence of an acid reaction on Congo, and allowed to stand for 1 hour. A colorless precipitate of the zinc mercaptide formed. The product was dried in a drying cabinet at 40°. The yield of the dry product was 10 g, or 94% of the theoretical. 10 g of the zinc salt of 5-trifluoromethyl-1,2-aminothiophenol was heated to boiling with 25 ml of acetic anhydride for 3 hours. The solution was placed into a flask for steam distillation, made weakly alkaline with ammonia, and the product steam distilled. The product crystallized from the distillate, was filtered and dried. After recrystallization from petroleum ether – white sheets with m.p. 63-64°.

Yield 62% of the theoretical.

Found %: N 6.63, 6.67. $C_9H_6NSF_3$. Calculated %: N 6.45.

The methiodide of 2-methyl-5-trifluoromethylbenzthiazole was obtained by heating 0.5 g of the base and 0.3 g of dimethyl sulfate on the boiling water bath for 3 hours. The product was washed with benzene and precipitated from an aqueous solution with potassium iodide. After recrystallization from aqueous alcohol, the yield was 0.72 g or 88% of the theoretical; m.p. 303-304°.

Found %: 35.60. $C_{10}H_9NSF_3$. Calculated %: 35.38.

The ethiodide of 2-methyl-5-trifluoromethylbenzthiazole was obtained by heating 3 g of the base and 2.25 g of diethyl sulfate on the boiling water bath for 7 hours. On the following day, the mass crystallized; it was dissolved in water. The unreacted 2-methyl-5-trifluoromethylbenzthiazole (0.25 g) was filtered off, and the iodide was precipitated from the solution with a solution of potassium iodide, the precipitated product was filtered, washed with water, benzene, and ether, and recrystallized from aqueous alcohol. Yield, 3.3 g or 70% of the theoretical; m.p. 197° with decomposition.

Found %: 33.82. $C_{11}H_{11}NSF_3$. Calculated %: 34.05.

2-Methyl-5-benzothiazolecarboxylic acid. a) A mixture of 0.3 g of 2-methyl-5-trifluoromethylbenzthiazole and 2 g of sulfuric acid (monohydrate) was heated in a test tube with an air condenser until hydrogen fluoride began to separate, which could be detected by the etching of the test tube and the formation of bubbles of gas. The heating was continued intermittently for 3 hours. After the separation of the bubbles of HF ceased, the reaction mixture was cooled, poured on ice, and made alkaline. Traces of the unreacted product were filtered, and the solution was acidified with acetic acid to a weakly acid reaction. The precipitate was filtered and recrystallized from aqueous methanol. Yield of colorless, long needles, 0.2 g or 77% of the theoretical; m.p. 202°.

Found %: N 7.42. $C_9H_7O_2NS$. Calculated %: N 7.25.

b) 3 g of 2-methyl-5-aminobenzthiazole was dissolved in 6 ml of concentrated hydrochloric acid and 4.5 ml of water, and was diazotized with cooling with 1.28 g sodium nitrite in 6 ml of water. The diazo compound was added in small portions to a solution of 5 g of $CuSO_4$ and 4.5 g of NaCN in 30 ml of water; the mixture was then heated for 1 hour on the boiling water bath. The solution was made alkaline, the precipitate was filtered, and washed with water, and the product extracted from it with boiling toluene. (3 times with 15 ml). The toluene solution was concentrated. The precipitated product was dissolved in aqueous alcohol. The yield of colorless 2-methyl-5-cyanobenzthiazole was 1.11 g or 35% of the theoretical; m.p. 156-157°.

Found %: N 16.11. $C_9H_6N_2S$. Calculated %: N 16.09.

0.2 g of 2-methyl-5-cyanobenzthiazole was boiled for 1.5 hours with 4.5 ml of concentrated sulfuric acid and 3 ml of water. After cooling, the mixture was diluted with water, made alkaline, filtered, and acidified with acetic acid to litmus. The precipitated acid was filtered and recrystallized from aqueous alcohol. Colorless needles with m.p. 203°. Yield 0.19 g or 86% of the theoretical. No depression was obtained upon a mixed melting point determination with the acid obtained by the hydrolysis of 2-methyl-5-trifluoromethylbenzthiazole.

Found %: N 7.36. $C_9H_7O_2NS$. Calculated %: N 7.25.

2-Methyl-5-fluorobenzthiazole. 5 g of 2-methyl-5-aminobenzthiazole was dissolved in 46 g of 40% fluoboric acid in a platinum dish, cooled well, and diazotized by the dropwise addition of a solution of 2.2 g of sodium nitrite in 5 ml of water. After standing for 45 minutes in a freezing mixture, the precipitated diazonium fluoborate was filtered, washed with alcohol, and ether, and dried for 24 hours in a vacuum desiccator. Decomposition temperature, 147°. Yield, 6.73 g or 84% of the theoretical.

6.5 g of the diazonium fluoborate was placed in a 250 ml round bottomed flask, and 50 ml of decalin was added to it. The flask was connected to a well cooled reflux condenser, and heated until the evolution of $BF_3$ ceased; the mixture was then heated for 10 minutes more. After cooling, the product was extracted from the decalin with 10% hydrochloric acid (3 times with 40 ml), and the aqueous layer separated. The last traces of decalin were steam distilled from the acidic solution; the solution was then neutralized with sodium carbonate, and the distillation resumed whereupon 5-fluoro-2-methylbenzthiazole distilled in the form of an oily liquid with the odor of a thiazole. The product was extracted with ether (3 times with 50 ml), the ether solution was dried with $MgSO_4$, the ether then removed, and the preparation vacuum distilled. Colorless, oily liquid with b.p. 110-112° at 7 mm. Yield 1.5 g or

30% of the theoretical based on the amine used; $n_D^{20}$ 1.5864.

Found %: N 8.53, 8.59. $C_8H_6NSF$. Calculated %: N 8.38.

The ethiodide of 2-methyl-5-fluorobenzthiazole was obtained by heating 1.25 g of the base and 1.25 g of diethyl sulfate on the boiling water bath. After 5 hours, the mixture crystallized. The yield of the benzene and ether-washed raw product was practically quantitative. The iodide was precipitated from an aqueous solution with potassium iodide. After recrystallization from aqueous alcohol, the yield was 1.9g or 75% of the theoretical; m.p. 195° with decomposition.

Found %: I 39.12, 39 26. $C_{10}H_{11}NSFI$. Calculated %: I 39.32.

DYES

Bis-[3-Ethyl-5-trifluoromethylbenzthiazole-(2)]trimethinecyanine iodide (I). 0.5 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide and 0.5 g of orthoformic ester were boiled for 30 minutes with 3.5 ml of acetic anhydride. The yield of the crude product was 0.26 g, after recrystallization from 60 ml of ethyl alcohol, the yield was 0.21 g, or 50% of the theoretical. Absorption maximum, 557 mμ; m.p. 269-270° with decomposition.

Found %: I 19.99, 19.91. $C_{23}H_{19}N_2S_2F_6I$. Calculated %: I 20.22.

Bis-[3-Ethyl-5-trifluoromethylbenzthiazole-(2)]-pentamethinecyanine iodide (II). 0.17 g of β-anilinoacroleinanil hydrochloride and 0.5 g of 2-methyl-5-trifluoromethylbenzthiazole methiodide were boiled for 20 minutes with 4 ml of acetic anhydride and 3 drops of pyridine. The precipitated dye was recrystallized from methyl alcohol. Green needles with m.p. 262-263° with decomp. Yield 0.21 g or 50% of the theoretical. Absorption maximum, 651 mμ.

Found %: I 19.11, 19.13. $C_{25}H_{21}N_2S_2F_6I$. Calculated %: I 19.41.

Bis-[3-Ethyl-5-trifluoromethylbenzthiazole-(2)]heptamethinecyanine iodide (III). 0.5 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide and 0.19 g of glutaconaldehydeanilanilide hydrochloride were dissolved by boiling in 5 ml of absolute alcohol; then a solution of 0.03 g of Na in 1.5 ml of absolute alcohol was added, and the mixture was boiled for 1 minute. The precipitated crystals were recrystallized from methyl alcohol. Yield 0.1 g or 22.2% of the theoretical. Bright green crystals with m.p. 158-159° with decomp. The absorption maximum of this dye is beyond the limits of the visual spectrum.

Found %: I 18.35. $C_{27}H_{23}N_2S_2F_6I$. Calculated %: I 18.67.

Bis-[3-Ethyl-5-trifluoromethylbenzthiazole-(2)]-9-methyltrimethinecyanine iodide (IV). 0.37 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide and 0.4 g of orthoacetic ester was heated for 40 minutes with 3 ml of acetic anhydride and 3 drops of pyridine. The precipitated dye was recrystallized from alcohol. Long violet needles with m.p. 288-289° with decomp. Yield 0.12 g or 37.5% of the theoretical. Absorption maximum, 544 mμ.

Found %: I 19.49. $C_{24}H_{21}N_2S_2F_6I$. Calculated %: I 19.77.

Bis-[3-Ethyl-5-trifluoromethylbenzthiazole-(2)]-9-ethyltrimethinecyanine iodide (V). 0.25 g of 2-methyl-5-trifluoromethylbenzthiazole and 0.2 g of diethyl sulfate were heated for 7 hours on the boiling water bath. The solidified salt was washed with benzene and ether, and dried; it was heated with 0.4 g of orthopropionic ester for 40 minutes in 3 ml of pyridine. The dye was precipitated with an aqueous solution of potassium iodide, and recrystallized from ethyl alcohol. Yield 0.08 g or 26%. Red violet needles with m.p. 216-218° with decomp. Absorption maximum, 550 mμ.

Found %: I 19.09. $C_{25}H_{23}N_2S_2F_6I$. Calculated %: I 19.37.

[3-Ethyl-5-trifluormethylbenzthiazole-(2)][1-ethylquinoline-(2)]trimethinecyanine iodide (VI). 0.42 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide, 0.5 g of 2-acetanilidovinylquinoline ethiodide, and 0.4 g of sodium acetate were heated for 30 minutes on the boiling water bath with 3 ml of acetic anhydride. The dye was precipitated with ether, filtered, washed with water, and recrystallized from 60 ml of alcohol. Yield 0.22 g or 35.4% of the theoretical; m.p. 276-277° with decomp. Absorption maximum, 570 mμ.

Found %: I 22.69. $C_{24}H_{22}N_2SF_3I$. Calculated %: I 22.96.

[3-Ethyl-5-trifluoromethylbenzthiazole-(2)][3-ethylbenzthiazole-(2)] methinecyanine iodide (VII). 0.2 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide, 0.18 g of 2-methylmercaptobenzthiazole ethiodide, and 0.1 g of anhydrous sodium acetate was boiled with 3 ml of absolute alcohol for 1 hour. After 2 recrystallizations from

alcohol, lemon yellow needles with m.p. 269-270° with decomp. were obtained. Yield 0.18 g or 65% of the theoretical. Absorption maximum, 425 mμ.

Found %: I 23.66. $C_{20}H_{18}N_2S_2F_3I$. Calculated %: I 23.78.

2-(3-Ethyl-5-trifluoromethylbenzthiazolenilidene-2'-ethylidene)-3-oxo-2,3-dihydrothionaphthene (VIII). 0.25 g of 2-methyl-5-trifluoromethylbenzthiazole ethiodide, 0.17 g of 3-hydroxythionaphthen-2-aldehyde anil, and 0.22 g of anhydrous sodium acetate were heated for 45 minutes with 3 ml of absolute alcohol. The precipitate was washed with water, and recrystallized from alcohol. Red violet needles with m.p. 294-296°. Yield 0.19 g or 70% of the theoretical. The preparation showed solvatochromism. Its absorption maximum in alcohol solution was 545 mμ, and in benzene, 520 mμ.

Found %: N 3.55. $C_{20}H_{14}ONS_2F_3$. Calculated %: N 3.45.

2-p-Dimethylaminostyryl-5-trifluormethylbenzthiazole ethiodide (IX). 0.3 g of trifluormethylbenzthiazole methiodide and 0.14 g of p-dimethylaminobenzaldehyde were boiled for 30 minutes with 3 ml of acetic anhydride. The precipitated dye was recrystallized from alcohol. Red-violet needles with m.p. 237-238°. Yield 0.22 g or 55% of the theoretical. Absorption maximum, 540 mμ.

Found %: I 24.89. $C_{20}H_{20}N_2SF_3I$. Calculated %: I 25.19.

Bis-[3-Ethyl-5-fluorobenzthiazole-(2)]trimethinecyanine iodide (X). 0.3 g of 2-methyl-5-fluorobenzthiazole ethiodide and 0.3 g of orthoformic ester were boiled for 20 minutes with 2 g of acetic anhydride. The precipitated dye was recrystallized from ethyl alcohol. Bronze needles with m.p. 288-289° with decomp. Absorption maximum, 562 mμ. Yield 0.15 g or 62 % of the theoretical.

Found %: I 24.32, 24.20. $C_{21}H_{19}N_2SF_2I$. Calculated %: I 24.05.

Bis-[3-Ethyl-5-fluoromethylbenzthiazole-(2)]-9-methyltrimethinecyanine iodide (XI). It was obtained from 0.5 g of 2-methyl-5-fluorobenzthiazole ethosulfate and 0.5 g of orthoacetic ester by heating for 30 min. with 3 g of pyridine and 3 drops of acetic anhydride. The ethiodide of the dye was precipitated with a solution of potassium iodide. Recrystallization from alcohol, the dye melted at 278-279° with decomp. Yield 0.15 g or 35% of the theoretical. Absorption maximum, 546 mμ.

Found %: I 23.14. $C_{22}H_{21}N_2S_2F_2I$. Calculated %: I 23.43.

Bis-[3-ethyl-5-flurobenzthiazole-(2)]-9-ethyltrimethinecyanine iodide (XII). 0.5 g of 2-methyl-5-fluorobenzthiazole ethosulfate and 0.5 g of orthopropionic ester were boiled for 40 minutes with 3 ml of acetic anhydride and 1 drop of pyridine. The dye was precipitated with ether from the solution, dissolved once more in a small amount of alcohol, and precipitated with potassium iodide. Yield after recrystallization from alcohol, 0.1 g or 23% of the theoretical; m.p. 255-256° with decomp. Absorption maximum, 550 mμ.

Found %: I 22.66. $C_{23}H_{23}N_2S_2F_2I$. Calculated %: I 22.84.

## SUMMARY

1. Some 2-methyl-5-trifluoromethyl- and 2-methyl-5-fluorobenzthiazoles and their quaternary salts were synthesized.

2. Nine thiacyanine dyes with a trifluoromethyl group in position 5 and three thiacyanine dyes with a fluorine atom in position 5 were prepared.

3. It was shown that the introduction of a fluorine atom or a $CF_3$- group into position 5 of the thiacyanine has almost no effect on the position of the absorption maximum.

4. 2-Methyl-5-cyanobenzthiazole and 2-methylbenzthiazole-5-carboxylic acids were synthesized.

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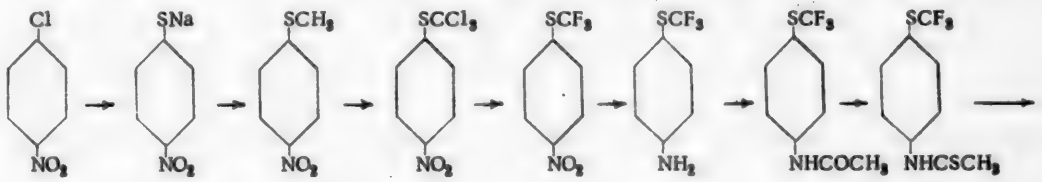
* See Consultants Bureau English translation, p. 2187.

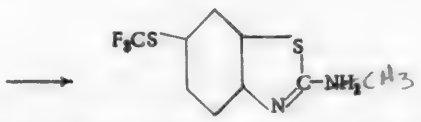
# CYANINE DYES CONTAINING FLUORINE

## III. CYANINE DYES FROM DERIVATIVES OF 6-TRIFLUOROMETHYLMERCAPTOBENZTHIAZOLE

L. M. Yagupolsky and A. I. Kiprianov

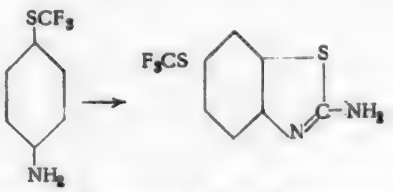
The compounds containing a trifluoromethylmercaptan group, $SCF_3$, are poorly studied. The methods of preparation and the properties of the substances of this class are given only in the patent literature [1] and are mentioned in certain communications [2,3], on the chemistry of fluoro-organic compounds. Dyes containing the $SCF_3$-group, according to the results in the patents, are outstanding in stability to light and in the brightness of color. The effect the $SCF_3$-group, as a substituent, on the color of the dyes has not been investigated. A series of thiocyanine dyes containing a $SCF_3$-group in the 6-position of the benzthiazole nucleus was synthesized. As the starting materials, 2-amino- and 2-methyl-6-trifluoromethylmercaptobenzthiazole, not reported in the literature, were obtained. The latter compounds were synthesized according to the following scheme:



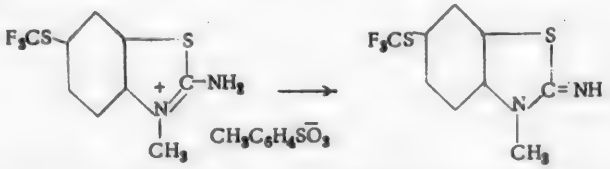




The methiodide of 2-methyl-6-trifluoromethylmercaptobenzthiazole and from it, the carbocyanine (I), the merocyanine (II), and the styryl dye (III) were prepared.

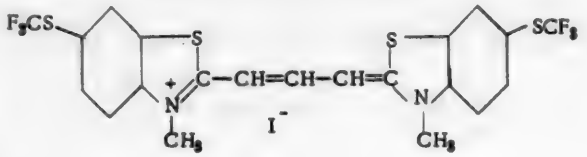
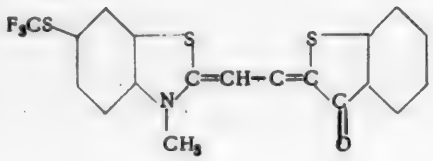
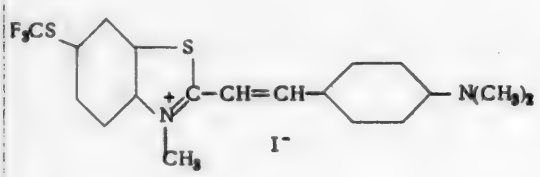
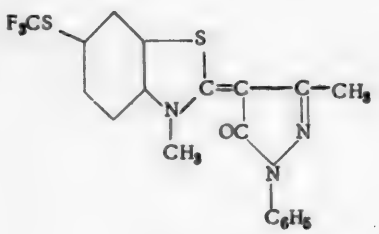
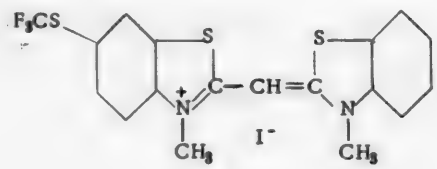
2-Amino-6-trifluoromethylmercaptobenzthiazole was obtained by the thiocyanation of p-aminophenyl-trifluoromethylsulfide:




The p-toluenesulfonate was obtained from the above amine, which was transformed by the action of alkali into the imine:




The imine was condensed with methylphenylpyrazolone and with 2-methylbenzthiazole methylmethosulfate [4,5]; the common merocyanine (IV) and monomethinecyanine (V) were obtained. The structural formulas and the absorption maxima of the dyes obtained in alcoholic solutions are listed in the table; the absorption maxima of the corresponding dyes without $SCF_3$ groups are given there for comparison.

| Expt. No. | Formula of dye | $\lambda_{max}$ (in mμ) | $\lambda_{max}$ of dye without $SCF_3$-group |
|---|---|---|---|
| I |  | 565 | 557 |
| II |  | 550 | 556 |
| III |  | 540 | 530 |
| IV |  | 430 | – |
| V |  | 430 | 422 |

It is apparent from the table that the carbocyanine with the $SCF_3$-group as a substituent is colored somewhat more intensely than the unsubstituted dye. The preparation, containing the $SCH_3$-groups in the 6,6'-positions has an absorption maximum at 581 mμ [6]. Therefore, in cyanine dyes, the $SCF_3$-group is a weaker auxichrome than the $SCH_3$-group.

## EXPERIMENTAL

p-Nitrophenylmethylsulfide was obtained by the methylation of sodium p-nitrothiophenolate. The latter was prepared from p-nitrochlorobenzene and $Na_2S_2$ [7]. The yield was 75% of the theoretical based on the p-nitrochlorobenzene used. The melting point of the product recrystallized from methyl alcohol was 72° [8].

p-Nitrophenyltrichloromethylsulfide. 16.5 g of p-nitrophenylmethylsulfide was dissolved in 40 ml of dry chloroform. The solution was cooled and dry chlorine was passed in for 1 hour in the light. The mixture was allowed to stand for 1 hour. The main part of the product crystallized. After the evaporation of the filtrate, some more of the product was obtained. The combined yield was 21.9 g or 81% of the theoretical, m.p. 92°. After recrystallization from acetone, m.p. 94°. This same melting point is reported in the communication of Zinke [9]; however, no details for the preparation of this substance are given.

p-Nitrophenyltrifluoromethylsulfide. A mixture of 12.5 g of p-nitrophenyltrichloromethylsulfide and 12 g of redistilled antimony trifluoride was placed in a Claisen flask and heated carefully with a naked flame until it melted. An exothermic reaction proceeded. As soon as the liquid started to boil, the flask was evacuated, and the distillation was continued until almost nothing distilled. The distillate was dissolved in a mixture of 50 ml of ether and an excess of 6 N HCl. The aqueous layer was separated, and the ether was washed several times with 6 N HCl until the wash liquid did not cloud up on dilution with water. The ether solution was dried over $MgSO_4$, the ether removed, and the residue vacuum distilled. p-Nitrophenyltrifluoromethylsulfide – a yellow liquid with b.p. 115° at 20 mm. Yield 7 g or 70% of the theoretical. The Beilstein test for halogen was negative. This preparation was mentioned in the patent [a]. Details of its preparation are not given in the patent.

p-Aminophenyltrifluoromethylsulfide. 6.4 g of p-nitrophenyltrifluoromethylsulfide was dissolved in 15 ml of alcohol and a solution of 34 g of stannous dichloride in 26 ml of concentrated hydrochloric acid was added stepwise with efficient stirring to the solution. The addition took 30 minutes. The temperature rose to 60-70°. When the exothermic reaction ceased, the solution was heated on the water bath for 30 minutes, then cooled and poured into a mixture of 120 g of ice and 100 ml of a 40% sodium hydroxide solution. The amine was extracted with three portions (of 35 ml) of ether. The ether solution was dried over $MgSO_4$, the ether removed and the residue distilled at reduced pressure. p-Aminophenyltrifluoromethylsulfide – a colorless liquid with b.p. 102-103° at 8 mm. Yield 4.7 g or 85.4% of the theoretical; $n_D^{25}$ 1.5253.

Found %: N 7.29, 7.36. $C_7H_6NSF_3$. Calculated %: N 7.22.

p-Acetaminophenyltrifluoromethylsulfide. 2.3 g (10% excess) of acetic anhydride was added dropwise with efficient stirring to 4 g of the amine. The mixture solidified, and was recrystallized from dilute alcohol. Long white needles with m.p. 185°. Yield 4.55 g or 95% of the theoretical.

Found %: N 6.05, 6.10. $C_9H_8ONSF_3$. Calculated %: N 5.95.

p-Thioacetylaminophenyltrifluoromethylsulfide. 3.5 g of p-acetylaminophenyltrifluoromethylsulfide was dissolved in a mortar with 2 g of phosphorus pentasulfide and melted on the water bath under a layer of toluene for 20 minutes with efficient stirring. The toluene layer was then decanted, and the residue was twice extracted from 20 ml of hot toluene. After cooling, yellowish crystals of the thioacetyl derivative separated from the toluene solution. The mother liquor was concentrated. For purification, the precipitated crystals were dissolved in dilute alkali and precipitated with carbon dioxide. Yield 2.4 g, or 65% of the theoretical. Recrystallized from aqueous alcohol, the preparation had the m.p. 119°.

Found %: N 5.71. $C_9H_8NS_2F_3$. Calculated %: N 5.57.

2-Methyl-6-trifluoromethylmercaptobenzthiazole. A cooled solution of 1.7 g p-thioacetylaminophenyltrifluoromethylsulfide in 22 ml of 2 N sodium hydroxide was added dropwise with stirring to 25 ml of a 20% solution of potassium permanganate placed in a round bottomed flask. After mixing both solutions, the stirring was continued for 30 minutes. On the following day, the solution was poured from the settled yellow oil which was washed several times with water and steam distilled from the same flask. After recrystallization from petroleum ether, white needles, m.p. 74°, with a pleasant odor, were obtained. Yield 0.6 g, or 35% of the theoretical.

Found %: N 5.65, 5.82. $C_9H_6NS_2F_3$. Calculated %: N 5.62.

2-Methyl-6-trifluoromethylmercaptobenzthiazole methiodide was obtained by heating 0.6 g of the base and 0.3 g of dimethylsulfate on the boiling water bath for 3 hours. The product was washed with benzene, and precipitated from an aqueous solution with potassium iodide. After recrystallization from aqueous alcohol, the yield was 0.8 g or 85% of the theoretical; m.p. 244-245° with decomp.

Found %: I 32.25, 32.29. $C_{10}H_5NS_2F_3I$. Calculated %: I 32.49.

2-Amino-6-trifluoromethylmercaptobenzthiazole. A solution of 0.8 g of bromine in 4 ml of glacial acetic acid was added dropwise with stirring to a solution of 1 g of p-aminophenyltrifluoromethyl sulfide and 1.6 g of ammonium thiocyanate in 10 ml of 98% acetic acid. The mixture was stirred for 5 hours and filtered. The residue on the filter was washed with water. The filtrate and the wash water were neutralized with ammonia. The precipitate was filtered and dried. M.p. 148°. Yield 0.97 g or 75% of the theoretical. For analysis the product was dissolved in a small amount of alcohol and precipitated in the form of the hydrochloride salt by the addition of an equal volume of concentrated hydrochloric acid. The hydrochloride was dissolved in water, filtered, and the amine precipitated with ammonia. After 2 recrystallizations from aqueous alcohol, white crystals with m.p. 153-154° were obtained.

Found %: N 11.28, 11 36. $C_8H_5N_2S_2F_3$. Calculated %: N 11.20.

The acetyl derivative was obtained by heating 1 g of the amine and 0.5 g of acetic anhydride in 5 ml of xylol to boiling for 3 hours. The product which crystallized upon cooling, was recrystallized from alcohol; m.p. 214-215°. Yield 1.04 g or 90% of the theoretical.

Found %: N 9.56, 9.60. $C_{10}H_7ON_2S_2F_3$. Calculated %: N 9.58.

2-Amino-6-trifluoromethylmercaptobenzthiazole p-toluenesulfonate was obtained by melting 0.27 g of 2-amino-6-trifluoromethylmercaptobenzthiazole with 0.22 g methyl p-toluenesulfonate for 30 minutes at 140° on the oil bath. The product, washed with benzene, was recrystallized from 8 ml of water. White long needles with m.p. 259-260°. Yield 0.38 g of 79.5% of the theoretical.

Found %: N 6.61. $C_{16}H_{15}O_3N_2S_3F_3$. Calculated %: N 6.45.

6-Trifluoromethylmercapto-N- methylbenzthiazolonimine. 0.38 g of 2-amino-6-trifluoromethylmercaptobenzthiazole p-toluenesulfonate was dissolved in 10 ml of water and 2 N alkali was added stepwise to the warm solution until alkaline to litmus. The imine came out in the form of yellow, finely crystalline powder. Yield 0.18 g or 78% of the theoretical. After recrystallization from petroleum ether, m.p. 94°.

Found %: N 10.73, 10.76. $C_9H_7N_2S_2F_3$. Calculated %: N 10.60.

DYES

Bis-[3-methyl-6-trifluoromethylmercaptobenzthiazole-(2)]-trimethinecyanine iodide (I). 0.3 g of 2-methyl-6-trifluoromethylmercaptobenzthiazole and 0.3 g of orthoformic ester were boiled with 3 ml of acetic anhydride for 45 minutes. Yield, after recrystallization from alcohol, 0.15 g or 60% of the theoretical. Absorption maximum 565 mμ. Violet needles, m.p. 270-271° with decomp.

Found %: I 18.84, 18.90. $C_{21}H_{15}N_2S_4F_6I$. Calculated %: I 19.12.

2-(3'-Methyl-6'-trifluoromethylmercaptobenzthiazolenylidene-2-ethylidene)-3- oxo-2,3-dihydrothionaphthene (II). 0.25 g of 2-methyl-6-trifluoromethylmercaptobenzthiazole methiodide, 0.16 g of 3-hydroxythionaphthene-2-aldehyde anil, and 0.2 g of anhydrous sodium acetate were heated for 45 minutes with 4 ml of absolute alcohol. The precipitate was washed with water and recrystallized from alcohol. Red-violet needles with m.p. 298-300° with decomp. Yield 0.14 g or 51.8% of the theoretical. The preparation exhibits solvatochromatism. Its absorption maximum in alcohol solution was 550 mμ, and in benzene, 525 mμ.

Found %: N 3.19, 3.26. $C_{19}H_{12}ONS_3F_3$. Calculated %: N 3.31.

2-p-Dimethylaminostyryl-6-trifluoromethylmercaptobenzthiazole methiodide. 0.25 g of 2-methyl-6-trifluoromethylmercaptobenzthiazole methiodide and 0.1 g of p-dimethylaminobenzaldehyde were boiled with 3 ml of acetic anhydride for 45 minutes. The precipitated dye was recrystallized from alcohol. Long red-violet needles with m.p. 235-236° with decomp. Yield 0.23 g or 70% of the theoretical. Absorption maximum 540 mμ.

Found %: I 22.11, 22.17. $C_{19}H_{13}N_2S_2F_3I \cdot C_2H_5OH$. Calculated %: I 22.36.

According to analysis the dye contains 1 molecule of alcohol of crystallization.

4-(3-Methyl-6'-trifluoromethylmercaptobenzthiazolenylidene-(2')-(1-phenyl-3-methylpyrazolone-5)(IV). 0.16 g of 6-trifluoromethylmercapto-N-methylbenzthiazolonimine and 0.12 g of 1-phenyl-3-methylpyrazolone-5 were melted together for 30 minutes at 150° under a water vacuum. The reaction product was dissolved in alcohol by heating, filtered, cooled, and the precipitated dye recrystallized from alcohol once more. Yellow needles. Yield 0.18 g or 64% of the theoretical; m.p. 174-175°.

Found %: N 10.02, 10.14. $C_{19}H_{14}ON_3S_2F_3$. Calculated %: N 10.00.

3-Methyl-6-trifluoromethylmercaptobenzthiazolo-(2)-3-methylbenzthiazole(2')-methinecyanine iodide (V). 0.1 g of 6-trifluoromethyl-N-methylbenzthiazolonimine and 0.12 g of 2-methylbenzthiazole methylmethasulfate were melted together for 15 minutes at 175° under water pump vacuum. Toward the end of the reaction, the melt stopped foaming and solidified. The reaction product was washed several times with acetone. The dye was dissolved in alcohol, its iodide precipitated with potassium iodide, and then washed with water on the filter and recrystallized from 60 ml of alcohol. Yellow needles. Yield 0.12 g or 60% of the theoretical; m.p. 263-264° with decomp.

Found %: I 23.29, 23.37. $C_{18}H_{14}N_2S_3F_3I$. Calculated %: I 23.60.

## SUMMARY

1. 2-Methyl- and 2-amino-6-trifluoromethylmercaptobenzthiazole and a series of intermediate products, necessary for their preparation, were synthesized.

2. The quaternary salts of the above bases and the 5-thiacyanine dyes containing a $SCF_3$-group in the 6-position of the benzthiazole nucleus were obtained.

3. The $SCF_3$-group as a substituent in cyanine dyes is a weaker auxichrome than the $SCH_3$-group.

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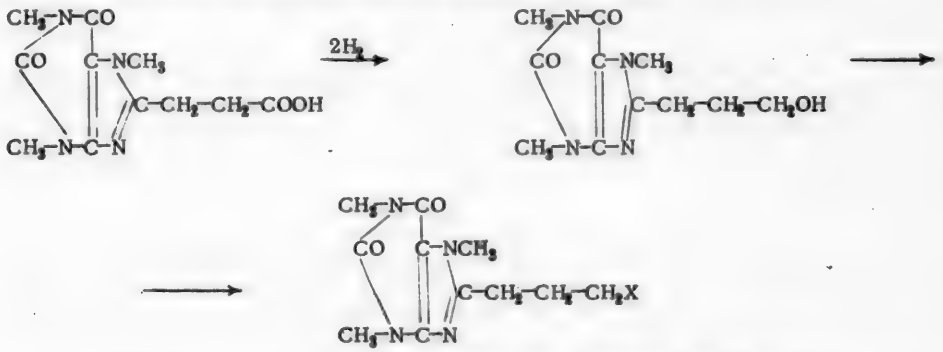
# 8- SUBSTITUTED DERIVATIVES OF METHYLATED XANTHINES

## IV. 8-(3-HYDROXYPROPYL)-CAFFEINE

E. S. Golovchinskaya and E. S. Chaman

The starting material for the synthesis of 8-(3-hydroxypropyl)-caffeine was β-(caffeine-8)-propionic acid [1] which was reported in the previous communication. Further transformations of 8-(3-hydroxypropyl)-caffeine resulting from the reduction of this acid, created a possibility for obtaining an entire group of caffeine derivatives substituted in position 8 with a three-membered hydrocarbon residue:



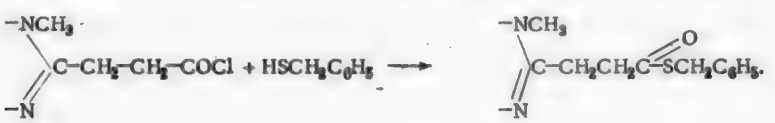
X = halide, $NR_2$, H, OCOR, OR, and others.

The choice of a method for reducing β-(caffeine-8)-propionic acid into 8-(3-hydroxypropyl)-caffeine was for the most part limited by the chemical properties of caffeine. Its sensitivity to alkalies exempted the use of the reduction reaction with sodium in alcohol which is widely applied in similar cases in laboratory practice. The tendency of xanthines to be transformed into desoxyxanthines during electrochemical reduction [2], as well as the hydrogenation of the ring during catalytic reduction of the carbonyl group which needs high temperature and pressure, did not permit the use of these two convenient methods for the transformation of acids into derivatives of the corresponding alcohols.

In view of the problem posed in the present investigation, the reduction of β-(caffeine-8)-propionic acid, the method of Prelog et al [3] published in 1946 for the preparation of alcohols from esters of certain thiolcarboxylic acids by means of reductive desulfurization with large excess of Raney nickel in dry solvent media at room temperature, became of great interest. The results of these authors appeared to conflict, without reason, with results published almost at the same time in the communication of Wolfram and Carabinos [4] reporting the production of aldehydes, not alcohols from thiolcarboxylic esters under analogous conditions differing only in the use of 70-80% alcohol, instead of a dry solvent, higher reaction temperatures (70-80°), and a smaller amount of Raney nickel.

The attempted application of the reductive desulfurication had beside the main task, the preparation of 8-(3-hydroxypropyl)-caffeine, two more: to clarify the possibility of extending this reaction to a series of (caffeine-8)-alkylcarboxylic acid, and to study the question of which variation in the conditions of reduction determines the formation of the alcohol and the aldehyde.

The thiol ester of β-(caffeine-8)-propionic acid used as the starting material was the benzyl ester. It was obtained in good yield by the reaction of the acid chloride with benzyl mercaptan.



Experiments on the reduction of this ester under various conditions gave identical results. Whether the ester was stirred for 2 hours in absolute dioxane solution with 12 parts by weight of Raney nickel without heating, or heated for 16 hours with 5 parts of Raney nickel in 80% alcohol solution, only one substance was obtained, m.p. 89-91°, crystallizing from ethyl acetate as fine needles.

The same substance, but in a mixture with the unreacted starting material, was obtained in a reaction with a smaller amount (2.5 parts by weight) of Raney nickel. This substance, as shown by analysis as well as chemical properties, was 8-(3-hydroxypropyl)-caffeine. Caffeine-8-propionaldehyde was not obtained in any of the experiments conducted. Upon the study of the mother liquor after the separation of 8-hydroxypropylcaffeine, not even traces of the aldehyde could be detected by qualitative reactions. From these solutions, in all of the experiments conducted, i.e., under various reduction conditions, a crystalline substance with m.p. 186-187° was isolated, which on further study, was shown to be 8-ethylcaffeine [5].

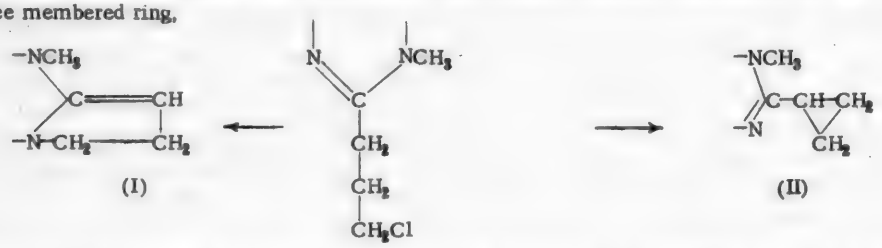
8-(3-Hydroxypropyl)-caffeine, obtained in the above reduction reactions, was characterized by the formation of an acetate. 8-(3-chloropropyl)-caffeine was also obtained from it by heating with thionyl chloride in absolute benzene. The use of an excess of thionyl chloride in this case, did not lead to further chlorination of the hydrocarbon chain, as had taken place during the preparation of the acid chloride of β-(caffeine-8)-propionic acid [1].

The halogen in 8-(3-chloropropyl)-caffeine was shown to be considerably less active than in 8-chloromethylcaffeine. Diethylaminopropylcaffeine was obtained in satisfactory yield only after a prolonged period of heating to 120-130° with diethylamine in a sealed tube, whereas, in the case of chloromethylcaffeine, this reaction proceeded readily with high yield even after 4 hours of moderate heating on the water bath with excess diethylamine [6].

An attempt to prepare the ethyl ether from chloropropylcaffeine and sodium ethylate led to the formation of two substances. One of these, moderately soluble in organic solvents and purified by several recrystallizations from alcohol, melted at 172-174°, and, according to analysis, did not contain an ethoxyl or halogen. After its recrystallization, a second substance was isolated from the mother liquor [apparently the ethyl ether of 8-(3-hydroxypropyl)-caffeine], very soluble in all organic solvents, with m.p. 82-84°, which could not be easily purified to give a satisfactory analysis because of its great solubility. The results of the elementary analysis for this substance with m.p. 172-174° almost coincided with those calculated for 8-propylcaffeine. On the other hand, this substance was sharply differentiated from 8-propylcaffeine [previously synthesized by one of the authors [7]],by its melting point (m.p. of 8-propylcaffeine, 116-117°) and other properties.

The absence of a double bond in the side chain, shown by the reactions – attempts at hydrogenation, oxidation with $KMnO_4$, and addition of bromine- excluded the plausible hypothesis of the cleavage to form 8-allylcaffeine.

Two other possibilities, the elimination of the hydrogen chloride accompanied by the closing of a five or three membered ring,

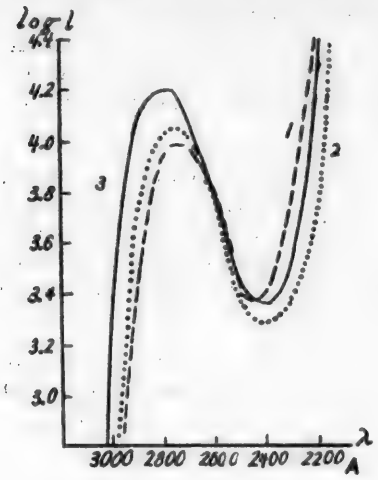



(I) (II)

were examined by comparing the ultra-violet absorption spectra of the compound obtained, 8-propylcaffeine, and caffeine (See Figure 1•). This comparison showed that although the maximum in the absorption spectrum of the substance studied is shifted toward the longer wavelengths by 50 A, and the intensity of absorption 1.5 times in comparison to the spectrum of caffeine), the general character of the spectrum of each of the three substances differs little. The resemblance of the spectra of these compounds excluded the possibility of the closing of a five membered ring. The formation of a complex three membered ring system (II) accompanied by a rearrangement

• The spectral analysis of this compound was made in the Inorganic and Physico-chemical laboratory by the senior scientific technician Yu. N. Sheinker and the chemist B. M. Golovner, to whom the authors express their sincere appreciation.

of the double bond from the imidazole part of the molecule to the side chain would have caused a much more significant change in the absorption spectrum.




1) Caffeine; 2) propylcaffeine; 3) substance studied.

The observed insignificant differences between the spectrum of the substance investigated and that of the other derivatives of caffeine, does not exclude the formation of a double bond in the propyl residue or the formation of a three membered ring (II). The absence of a double bond, shown by the chemical reactions of the substance, combined with the ultra violet absorption spectrum, results, of analysis, and other properties, gave a basis for considering that it was probably 8-cyclopropylcaffeine (II).

For the final proof that the substance obtained as a result of the reduction of the thiol ester of β-(caffeine-8)-propionic acid was 8-(3-hydroxypropyl)-caffeine, it was transformed into 8-propylcaffeine. Its chloroderivative was dehydrohalogenated by heating with an excess of Raney nickel in alcoholic solution in the presence of an equimolecular amount of alkali (8). A substance with m.p. 116-117° identical with the 8-propylcaffeine present for comparison was obtained.

The authors gratefully thank Prof. O. Yu. Magidson for the interest he has shown in the above investigation.

## EXPERIMENTAL

Benzyl β-(caffeine-8)-thiolpropionate. 30 g of caffeine propionic acid, 15 g of thionyl chloride, and 200 ml of dry benzene were stirred under reflux until complete solution of the acid, and the heating was continued for 30 min. 26 g of benzyl mercaptan was added with continuous stirring to the cooled reaction mixture, and after 5-10 min., 30 ml of pyridine. The reaction was continued for 24 hours at room temperature. The precipitate was filtered, washed with cold benzene, water, and ether. Weight 9 g; m.p. 126-127°. The benzene and pyridine were removed in vacuum from the solution. The residue was treated with ether. The crystals were filtered, washed with ether, and cold acetone. Weight 25.3 g, m.p. 124-126°. The combined yield of the ester was 34.3 g which corresponds to 81.6% of the theoretical. White oily needles, m.p. 126-127° readily soluble in the cold in chloroform, dioxane, and benzene. The ester is recrystallizable from ethyl alcohol −1:40, acetone −1:5, methyl ethyl ketone −1:7; it is insoluble in water and ether.

6.324 mg substance: 6.73 ml 0.01 N $H_2SO_4$. 5.761 mg substance: 6.12 ml 0.01 N $H_2SO_4$. Found %: N 14.90, 15.06. $C_{18}H_{20}O_3N_4S$. Calculated %: N 15.05.

8-(3-Hydroxypropyl)-caffeine. 1.) 30 g of Raney nickel was added to a solution of 5 g of benzyl-β-(caffeine-8)-thiolpropionate in 50 ml of dry dioxane, and the mixture stirred for 2 hours. An increase of 10-12° in temperature occurred. The settled solution was decanted, and the catalyst washed 3-4 times with dioxane. The dioxane was removed from the combined solutions, and the viscous residue crystallized by the addition of 1.5-2 ml of cold ethyl acetate. Recrystallized from ethyl acetate. Weight 1.7 g which corresponds to 55% of the theoretical. White needles with a faint pearly sheen, m.p. 88-91°, readily soluble in cold dioxane, acetone alcohol, and chloroform. Recrystallizable from benzene −1:10, ethyl acetate −1:5. It crystallized from xylol in the form of chains of needles.

5.502 mg substance: 8.57 ml 0.01 N $H_2SO_4$. 5.628 mg substance: 8.77 ml 0.01 N $H_2SO_4$. 4.639 mg substance: 8.789 mg $CO_2$; 2.800 mg $H_2O$. 3.176 mg substance: 6.022 mg $CO_2$; 1.912 mg $H_2O$. Found %: C 51.66, 51.71; H 6.75, 6.73; N 21.81, 21.81. $C_{11}H_{16}O_3N_4$. Calculated %: C 52.39.; H 6.35; N 22.22.

The ethyl acetate was completely removed from the filtrate, after the removal of the hydroxylpropylcaffeine, and the residue cooled. Cyrstals separated which, after recrystallization from acetone, melted at 186-187°.

4.164 mg substance: 8.347 mg $CO_2$; 2.356 mg $H_2O$. 4.968 mg substance: 8.88 ml 0.01 N $H_2SO_4$. 5.038 mg substance: 9.07 ml 0.01 N $H_2SO_4$. Found %: C 54.67; H 6.33; N 25.02, 25.20. $C_{10}H_{14}O_2N_4$. Calculated %: C 54.05; H 6.36; N 25.22.

Mixed m.p. determination with 8-ethylcaffeine – 186-187°.

2.) A solution of 3.4 g of benzyl β-(caffeine-8)-thiolpropionate in 136 ml of 80% alcohol was boiled with 17 g of Raney nickel for 6 hours on the water bath. It was filtered, and the alcohol was removed. The residue, after recrystallization from ethyl acetate, was 1.05 g; m.p. 79-81°. Mixed with 8-(3-hydroxypropyl)-caffeine, it melted at 79-81°. From the ethyl acetate filtrate, after the removal of the solvent, 0.25 g of a substance with m.p. 134-171° was obtained which melted at 184-186° after recrystallization from acetone. A mixture with 8-ethylcaffeine melted at 184-186°.

3.) A solution of 2.5 g of the thiol ester in 100 ml of 80% alcohol was boiled for 6 hours with 6.5 g of Raney nickel. It was filtered, and the alcohol removed to a volume of 13-15 ml. After cooling, 0.35 g of the initial thiol ester with m.p. 122-124° precipitated. The solvent was removed to dryness from the filtrate, after the removal of the unreacted ester, the residue treated with hot ethyl acetate, and filtered from a small amount of solid residue. The residue, after the removal of the ethyl acetate – 0.8 g, m.p. 63-73°; after several recrystallizations from ethyl acetate, it melted at 88-90°. Mixed m.p. with 8-(3-hydroxypropyl)-caffeine – 88-91°.

Acetate of 8-(3-hydroxypropyl)-caffeine. 0.55 g of 8-(3-hydroxypropyl)-caffeine was heated for 1.5 hours with 3 g of acetic anhydride. The acetic anhydride was removed in vacuum, the residue treated with water, and neutralized with dry sodium bicarbonate. Wt. 0.6 g; m.p. 136-138°. Yield 93.7% of the theoretical. White needles recrystallizable from ethyl acetate, alcohol, and benzene; insoluble in water.

6.659 mg substance: 9.00 ml 0.01 N $H_2SO_4$. 6.707 ml substance: 9.04 ml 0.01 N $H_2SO_4$. Found %: N 18.92, 18.87. $C_{13}H_{18}O_4N_4$. Calculated %: N 19.04.

8-(3-Chloropropyl)-caffeine. A solution of 5.5 g of hydroxypropylcaffeine in 60 ml of absolute benzene was heated for 6 hours with 3 ml of thionyl chloride. The benzene was removed, and the residue treated with cold sodium bicarbonate solution. The filtered substance was recrystallized from ethyl acetate. Weight – 3.6 g which corresponds to 62% of the theoretical. Transparent light greenish-yellow prisms with m.p. 117-118°, readily soluble in the cold in benzene and ether. It crystallized from alcohol as coarse platelets, ethyl acetate – transparent, coarse crystals.

4.327 mg substance: 2.314 mg AgCl. 5.437 mg substance: 2.872 mg AgCl. Found %: Cl 13.23, 13.07. $C_{11}H_{15}O_2N_4Cl$. Calculated %: Cl 13.12.

8-(3-Diethylaminopropyl)-caffeine. 3 g of 8-chloropropylcaffeine was heated for 12 hours in a closed tube with 30 ml of freshly distilled diethylamine at 120-130° bath temperature. After cooling, the diethylamine hydrochloride was filtered off, and the excess diethylamine removed in vacuum. The residue, a yellow oil, was dissolved in ether, filtered, and the diethylaminopropylcaffeine hydrochloride precipitated by the addition of an alcoholic hydrogen chloride solution until acid on Congo. It was recrystallized from absolute alcohol. Weight 2.5 g which corresponds to 66% of the theoretical.

Transparent, scaly platelets with m.p. 236-238°, readily soluble in water, and insoluble in organic solvents.

5.882 mg substance: 2.430 mg AgCl. 6.452 mg substance: 2.666 mg AgCl. Found %: Cl 10.22, 10.22. $C_{15}H_{25}O_2N_5 \cdot HCl$. Calculated %: Cl 10.33.

The 8-diethylaminopropylcaffeine base was liberated from an aqueous solution of the hydrochloride with 26% alkali solution, and extracted with ether. After the removal of the ether, the crystallized residue was recrystallized from pentane. White, light needles with m.p. 72-74°; readily soluble in cold alcohol, ether, chloroform, benzene, and water.

5.604 mg substance: 7.43 ml 0.01 N $H_2SO_4$. 4.498 mg substance: 7.24 ml 0.01 N $H_2SO_4$. Found %: N 22.59, 22.53. $C_{15}H_{25}O_2N_5$. Calculated %: N 22.80.

8-Propylcaffeine. A solution of 0.3 g of 8-chloropropylcaffeine and 0.07 g of potassium hydroxide in 4 ml of 80% alcohol was heated with 3 g of Raney nickel for 4 hours on the boiling water bath. 0.25 g of 8-propylcaffeine, with m.p. 105-106° was isolated from the filtered solution after removal of the alcohol. After recrystallization from methyl alcohol, m.p. 114-115°. After one more recrystallization, m.p. 116-117°. Mixed with 8-propyl caffeine, it melted at 116-117°.

Heating of 8-(3-chloropropyl)-caffeine with sodium ethylate. 1 g of chloropropylcaffeine was added to a solution of 0.09 g of Na in 20 ml of alcohol (99.7%), and the mixture boiled for 4 hours. The alcohol was removed, and the residue treated with ether. Insoluble in ether, 0.35 g with m.p. 165-167°. After several recrystallizations

from methyl alcohol, m.p. 172-174°. Coarse needles, readily soluble in benzene, ethyl alcohol, and chloroform; slightly soluble in ether, and insoluble in pentane.

4.349 mg substance: 7.40 ml 0.01 N $H_2SO_4$. 4.620 mg substance: 7.91 ml 0.01 N $H_2SO_4$. 3.459 mg substance: 7.162 mg $CO_2$; 1.801 mg $H_2O$. 0.1909 g substance: 15.2694 g benzene: $\Delta t$ 0.27°. Found %: C 56.46; H 5.82; N 23.82, 23.97. M 237.57. $C_{11}H_{14}O_2N_4$ (caffeine-cyclopropane). Calculated %: C 56.17; H 6.37; N 23.74. M 234.1.

0.5 g of a white substance which had the m.p. 82-84° after 4 recrystallizations from a mixture of carbon tetrachloride and pentane, was isolated from the ether solution. Readily soluble in ether, benzene, alcohol, ethyl acetate, acetone, methyl ethyl ketone, chloroform, and carbon tetrachloride.

5.476 mg substance: 6.61 ml 0.01 N $H_2SO_4$. 3.695 mg substance: 5.41 ml 0.01 N $H_2SO_4$. 3.832 mg substance: 2.91 ml $^1/_{50}$ N $Na_2S_2O_3$. Found %: N 20.67, 20.49; $C_2H_5O$ 11.40. $C_{13}H_{20}O_3N_4$ [8-(3-ethoxypropyl)-caffeine]. Calculated %: N 20.00; $C_2H_5O$ 16.07.

## SUMMARY

1. The reductive desulfurization reaction of thiolcarboxylic esters with Raney can be applied to (caffeine-8)-alkylcarboxylic acids.

2. The final result of the reductive desulfurization reaction of benzyl β-(caffeine-8)-thiolpropionate with Raney nickel was the alcohol, not the aldehyde.

3. Benzyl β-(caffeine-8)-thiolpropionate, 8-(3-hydroxypropyl)-caffeine, 8-(3-chloropropyl)-caffeine, the acetate of 8-(3-hydroxypropyl)-caffeine, and 8-(3-dimethylaminopropyl)-caffeine (hydrochloride and base) were synthesized and reported.

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* See Consultants Bureau English translation, p. 593.
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# 8-SUBSTITUTED DERIVATIVES OF METHYLATED XANTHINES

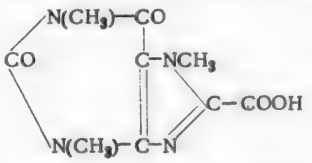
## V. REDUCTIVE DESULFURIZATION OF CAFFEINE 8-CARBOXYLIC ACID THIOL ESTERS

E. S. Golovchinskaya and E. S. Chaman

In the previous communication [1], the reductive desulfurization of benzyl β-(caffeine-8)-thiolpropionate by the action of Raney nickel was reported. The final result of this reaction was shown to be 8-(3-hydroxypropyl)-caffeine. As the side product, independent of the temperature, the absence or presence of moisture, and the amount of Raney nickel used, 8-ethylcaffeine was invariably isolated. The formation of 8-caffeinepropionaldehyde was not detected in any of the experiments conducted.

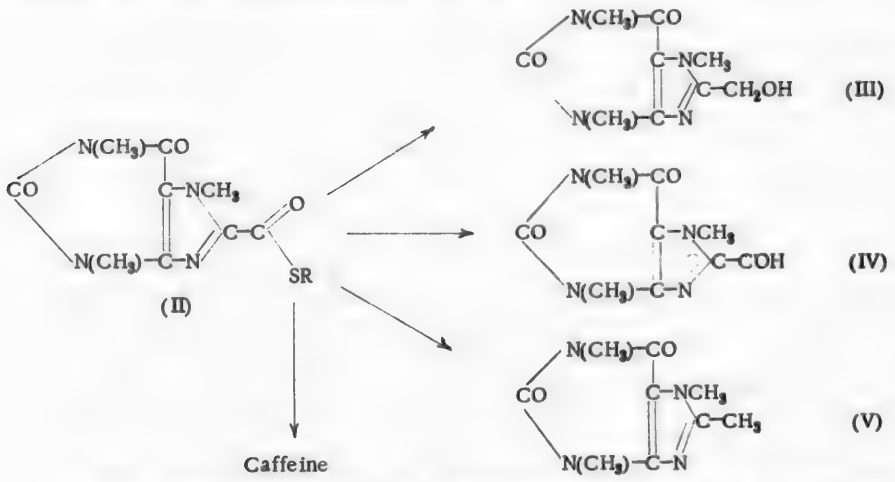
The study of this reaction with other examples of caffeine derivatives substituted by the thiolcarboxylic group in position 8, was undertaken in order to elucidate in more detail the process of reductive desulfurization, and in particular, to explain the reason for the elimination of the entire thiolcarboxylic group leading to the formation of a compound with a shorter hydrocarbon chain.

Caffeine 8-carboxylic acid (1) served as the starting material for this investigation.




(I)

In spite of the fact that the acid readily eliminates carbon dioxide in contrast to the very stable β-(caffeine-8)-propionic acid, it was used as the model for a detailed study of the reductive desulfurization because known compounds, which have been previously synthesized by one of us, and are available for comparison, would be formed as a result of any reduction of its thiol ester (II) – 8-hydroxymethylcaffeine (III), 8-caffeine-aldehyde (IV) as well as 8-methylcaffeine (V), and caffeine.

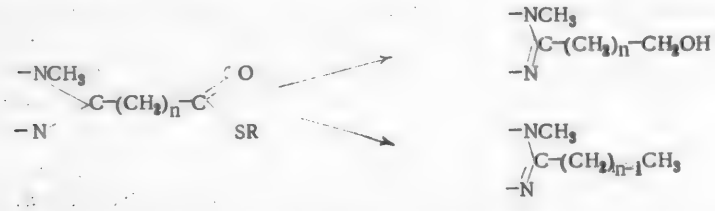



Benzyl caffeine-8-thiolcarboxylate was obtained, as was the ester of caffeine thiolpropionate, by the reaction of the acid chloride with benzyl mercaptan.

The reduction reaction of benzyl caffeinethiolcarboxylate, which was effected by means of 12 parts by weight of Raney nickel in dry dioxane medium, led to the formation of a mixture of two substances. A small

amount of a substance, poorly soluble in cold chloroform with m.p. 224° identified as 8-hydroxymethylcaffeine and the main product of the reaction, which was very soluble in chloroform, unsubstituted caffeine, were isolated from the mixture. Pure caffeine, in a yield of 89% of the theoretical, was obtained upon heating the thiolester with 6 parts by weight of Raney nickel in an 80% alcohol medium. 8-Hydroxymethylcaffeine could not be detected in this reaction. As with the reduction of the thiol ester of caffeine propionic acid, no traces of the aldehyde could be detected in the reaction mixtures of any of the reduction reactions.

The formation of 8-ethylcaffeine upon the reduction of the thiol ester of the very stable β-(caffeine-8)-propionic acid, and caffeine upon the reduction of the readily decarboxylated caffeine-8-carboxylic acid, showed that a reaction leading to the shortening of the hydrocarbon chain by one carbon atom takes place at the same time as the reductive desulfurization leading to the formation of the corresponding alcohols upon the action of the Raney nickel.

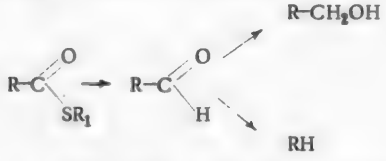


The second reaction, as a rule, apparently accompanies the reduction of the thiol ester of caffeine carboxylic acids wherein, in its role as the main or side product depends on the stability of the acid used.

The results obtained from two examples of caffeine carboxylic acids do not give any basis for supposing that the observed elimination is the usual reaction which accompanies the reductive desulfurization of thiol esters of all acids by the action of Raney, nor can this suggestion be excluded because, in the articles cited in the previous communication by Prelog et al, and Wolfram and Carabinos [2] on the reductive desulfurization of thiol esters, there is no mention made of the recovery of the unreacted part of the starting ester while the yields obtained are not always satisfactory (from 22-60% of the theoretical).

The suggestion that the formation of caffeine and 8-ethylcaffeine occurred by the decomposition of the alcohol formed initially and, therefore, is a secondary reaction, was completely refuted by the experiment in which 8-hydroxymethylcaffeine was reacted for 2 hours with Raney nickel: 8-hydroxymethylcaffeine was recovered almost quantitatively from the reaction mixture. This process was also contradicted by the fact that, when the time of the reduction of thiol esters was increased, not even in one case did the process shift toward a decrease in the yield of the alcohol with a corresponding increase in the amount of the cleavage product.

If the reduction of thiol esters is pictured as occurring in two stages with the initial formation of the aldehyde, then the mechanism of the reaction can be considered as the decomposition of the pre-formed aldehyde, undergoing a transformation to the alcohol and a cleavage to the hydrocarbon simultaneously:



The validity of this view of the reaction mechanism was confirmed by experiments on the reaction of 8-caffeinealdehyde with Raney nickel. As a result of a 2.5 hour stirring of caffeine aldehyde in dioxane solution with 12 parts by weight of Raney nickel at room temperature, 8-hydroxymethylcaffeine in a yield of 40% of the theoretical was isolated from the reaction mixture. A mixture with m.p. 185-205° was obtained from the mother liquor, which by recrystallization from chloroform, was separated into 8-hydroxymethylcaffeine and unsubstituted caffeine. The caffeine obtained from this reaction confirmed the suggestion that derivatives with an aldehyde group in position 8 are capable of transformation into 8-hydroxyalkylcaffeine with the simultaneous partial cleavage. The probability is also strengthened that the reduction of caffeine-8-carboxylic esters occurs by means of a stage in which the aldehyde is formed, and that the initially formed aldehyde compounds, as intermediates, decompose and serve as a source of the compounds with the shortened hydrocarbon chain.

The authors express their sincerest gratitude to the director of the laboratory in which this investigation was conducted, Prof. O. Yu. Magidson.

## EXPERIMENTAL

Preparation of 8-caffeinecarboxylic acid chloride. 5 g of 8-caffeinecarboxylic acid and 6 ml of thionyl-chloride were heated for 6 hours at a bath temperature of 82-85°. The excess thionyl chloride was removed in vacuum, and the residue recrystallized once from dry benzene. Weight 2.5 g, m.p. 168-173°. Yellow crystals which clung to the walls of the crystallization flask*.

Benzyl 8-caffeinethiolcarboxylate. A solution of 1.5 g of unpurified caffeine carboxylic acid chloride in 20 ml of dry benzene was added dropwise with stirring in 5-10 min. to a solution of 2.2 g of benzyl mercaptan and 0.7 g of dry pyridine in 5-10 ml of dry benzene. The reaction mixture was stirred for 20 hours. The combined reaction time was 48 hours at room temperature. It was filtered, and the residue, a mixture of pyridine hydrochloride and the thiol ester, was washed with water and ether. Weight 0.8 g, m.p. 173-175°. Another 0.2 g of the thiol ester with m.p. 174.5-176° was isolated from the benzene solution. The combined yield was 1 g which corresponds to 50% of the theoretical based on the acid chloride used. Colorless, transparent prisms with m.p. 175-176°. The ester is readily soluble in the cold in chloroform and dioxane. It was recrystallizable from ethyl alcohol – 1:60, isopropyl alcohol – 1:70, butyl alcohol – 1:20, benzene 1:10; it was slightly soluble in ether and insoluble in water.

6.90 mg substance: 4.645 mg $BaSO_4$. 6.570 mg substance: 4.390 mg $BaSO_4$. 5.952 mg substance: 7.03 mg 0.01 N $H_2SO_4$ Found %: S 9.24, 9.17; N 16.53. $C_{16}H_{16}O_3N_4S$. Calculated %: S 9.32; N 16.28.

Reaction of benzyl 8-caffeine thiolcarboxylate with Raney nickel. 1) A solution of 1.5 g of benzyl 8-caffeinethiolcarboxylate in 15 ml of dry dioxane was stirred for 2 hours at room temperature with 18 g of Raney nickel (an increase of 9° in the temperature occurred). The residue, after filtration and removal of the dioxane, 0.7 g with m. p. 169-208°, was treated with 2 ml of cold chloroform and filtered. 0.1 g with m.p. 219-224° was filtered off. Mixed with 8-hydroxymethylcaffeine, it melted at 219-225°. 0.1 g of the substance with m.p. 219-224° was heated with thionyl chloride. After removal of thionyl chloride, it melted at 201-209°. After recrystallization from ethyl acetate, m.p. 208-211°. Mixed with 8-monochloromethylcaffeine, it melted at 212-214°.

2) A solution of 1 g of benzyl 8-caffeinethiolcarboxylate in 50 ml of 80% alcohol and 6 g of Raney nickel was heated for 5 hours on the water bath. The alcohol was removed from the filtered solution; the residue melted at 226-230°; melting point of a mixture with caffeine, 226-231°. Yield 0.56 g which corresponds to 89% of the theoretical.

Reaction of 8-hydroxymethylcaffeine with Raney nickel. 1 g of 8-hydroxymethylcaffeine was stirred with 50 ml of dry dioxane. A large part of the substance went into solution at room temperature. 10 g of Raney nickel was added. The stirring was continued for 2 hours, after which time, it was heated until complete solution of the 8-hydroxymethylcaffeine, filtered, and the catalyst washed with hot dioxane. The residue, after the removal of the dioxane, was 0.90 g of 8-hydroxymethylcaffeine with m.p. 222-224°.

Reaction of 8-caffeine aldehyde with Raney nickel. A solution of 8-caffeine aldehyde in 50 ml of dioxane and 12 g of Raney nickel was stirred for 2.5 hours at room temperature. Upon the addition of the Raney nickel, there occurred an increase of 5° in the temperature and a slow separation of crystals of 8-hydroxymethylcaffeine from the solution. The reaction mixture was heated to complete solution of the precipitated 8-hydroxymethyl caffeine, filtered, and the nickel washed with dioxane. From the combined dioxane solution, concentrated in vacuum to 20-25 ml volume, 0.4 g of 8-hydroxymethylcaffeine with m.p. 214-221° crystallized on cooling. After one recrystallization from alcohol, m.p. 223-224°. The residue from the final removal of the dioxane, 0.35 g with m.p. 185-205°, was treated with 2 ml of cold chloroform and 0.05 g more of a substance was isolated, which was shown to be 8-hydroxymethylcaffeine with m.p. 214-218° after one recrystallization from alcohol. The residue after removal of the chloroform, with m.p. 211-230°, was recrystallized from alcohol; m.p. 221-230°. Mixed with 8-hydroxymethylcaffeine, it melted at 176-185° with 8-caffeine aldehyde – 135-160°, and with caffeine – 227-230°. After two more recrystallizations from alcohol, m.p. 227-231°.

## SUMMARY

1. The reductive desulfurization reaction of thiol esters of caffeine-8-carboxylic acid in primary alcohols with Raney nickel, is accompanied by the formation of compounds in which the side chain is shortened by one carbon atom.

2. Derivatives of caffeine substituted in position 8 by an aldehyde residue, are transformed partially into

* Upon attempts to recrystallize further the acid chloride for analysis, a hydrolysis occurred; for this reason the preparation of the thiol ester was effected with unpurified acid chloride.

alcohols and partially cleaved at the carbon atom bond containing the carboxyl group by the action of Raney nickel.

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*See Consultants Bureau English translation, p. 2277.

# PREPARATION AND SEVERAL PROPERTIES OF γ-FURYL-α-ALKYLALLYL ALCOHOLS

A. A. Arsenyuk

In one of the author's investigations [1] it was shown γ-furylallyl alcohol, obtained from furfurol by means of furylacrolein, polymerizes to form brittle tars, viscous thick oils, or masses with clearly expressed elastic properties. Upon the acetylation of γ-furylallyl alcohol with acetic anhydride in the presence of fused sodium acetate, the acetate, which is a pleasant smelling liquid, was obtained.

The present communication is concerned with experiments on the synthesis of several γ-furyl-α-alkylallyl alcohols and their acetates. The large amount of available literature material on the derivatives of allyl alcohol showed that the most successfull method for the preparation of γ-furyl- α-alkylallyl alcohols would probably be that using organomagnesium compounds. This method will allow the preparation of unsaturated alcohols under mild conditions which is very important for the synthesis of γ-furyl-α-alkylallyl alcohols containing a double bond in the relatively unstable furane nucleus. Of the secondary unsaturated alcohols containing an allyl residue and a furane, only α-allylfurfuryl alcohol had been obtained by this method [2,3]. The synthesis of this compound was effected in one step i.e. by the direct action of a mixture of allyl bromide and furfurol on magnesium. As a result of this reaction, 78% of theory of a brown liquid product boiling at 90-100° at 15 mm was obtained; after four vacuum redistillations, a comparatively small amount of α-allylfurfuryl alcohol with b.p. 96-97° (21 mm) was obtained. There are no results on the synthesis of secondary γ-furyl-α-alkylallyl alcohols by means of organo-magnesium compounds from furfurylacrolien, but there is a large amount of material on the preparation of corresponding (containing a phenyl residue) derivatives of allylic alcohols from cinnamaldehyde [2,4,5].

The many different syntheses effected by means of organo-magnesium compounds, made it possible to establish certain rules which can be used to predict the course of the reaction. For the preparation of secondary alcohols from aldehydes, it is necessary to conduct the synthesis in ether at low temperatures, and to use an excess of the alkyl magnesium halide [5]. In addition, the manner of decomposition of the reaction product of the alkyl magnesium halide with the carbonyl compound is always important. This operation is of unusually great importance for the synthesis of γ-furyl-α-alkylallyl alcohols because the latter, by the action of acidic agents (especially sulfuric acid), can dehydrate, isomerize, and tar [6,7 and others]. A series of experiments showed that the above secondary alcohols are obtained in good yield by the decomposition of the reaction products with ice, followed by the addition of a solution of ammonium chloride.

The following γ-furyl-α-alkylallyl alcohols (Table 1) were obtained from furylacrolein and the corresponding alkyl halide by means of the organo-magnesium synthesis.

The γ-furyl-α-alkylallyl alcohols synthesized, after vacuum redistillation, were pale yellow, oil-like liquids (resembling glycerol in their consistancy), with a characteristic odor. At ordinary temperatures, they are readily soluble in benzene, acetone, and ether, somewhat less — in alcohol, and practically insoluble in water.

On storage, especially in poorly closed vessels, the yellow color of the alcohol increases slowly, and then becomes red; after an extended period of time, they are transformed into transparent, wine-red, thick, (viscous) products.

The corresponding acetates (Table 2) were obtained by the acetylation of the γ-furyl-α-alkylallyl alcohols with acetyl chloride in the presence of pyridine.

The latter, in freshly prepared state, have a slight yellow color, possess an individual (rather pleasant) odor, and are more fluid than the alcohols. With the passage of time, the color of the esters slowly intensifies and then becomes red; according to their consistency, they become less fluid.

## EXPERIMENTAL

### I. Synthesis of γ-furyl-α-alkylallyl alcohols

1. Preparation of γ-furyl-α-methylallyl alcohol. 24.4 g (0.2 mole) of furylacrolein dissolved in 125-150 ml of ether was added stepwise from a dropping funnel, while the reaction flask was cooled with a mixture of ice and water, to a solution of methyl magnesium iodide prepared from 5.84 g (0.24 mole) of magnesium and 35.60 g

(0.25 mole) of methyl iodide in 75 ml of dry ether. Upon the addition of each drop of the furylacrolein, the formation of a yellow precipitate occurred, which, upon mixing the reaction mixture, dissappeared. The ether solution of furylacrolein must be added very slowly dropwise to the methyl magnesium iodide, because on conducting the reaction more rapidly, a considerable increase in temperature occurs resulting in a decrease of the yield of the alcohol synthesized. In order to attain a more complete reaction, the mixture was heated on the water bath to weak reflux of the ether for 2 hours. The product of the reaction of methyl magnesium iodide and furylacrolein was first cooled below zero degrees and then decomposed by the stepwise addition of ice to the flask, to which a cooled 25% ammonium chloride solution was then added. The ether solution of the alcohol was separated from the water layer; the latter was extracted 2 times with 50-25 ml of ether. The solution of the alcohol and the ether extracts were combined and dried with fused potassium carbonate. The residue, after the removal of the ether, distilled at 117.5-118.5° at 20 mm. An insignificant amount of tar-like products remained in the distillation flask. The yield of the γ-furyl-α-methylallyl alcohol in several experiments varied from 75.2-79.5%.

TABLE 1

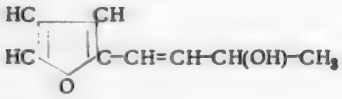
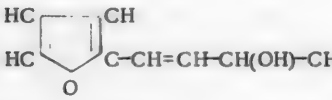
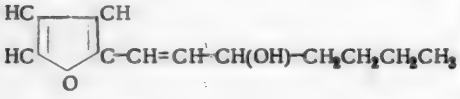
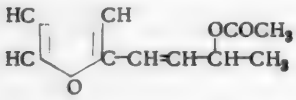
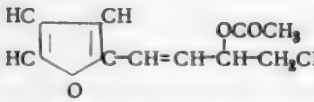
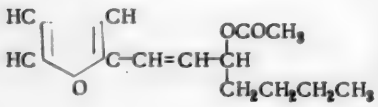
| Alcohols | Boiling points at 20 mm | $d_4^{20}$ | $n_D^{20}$ | $MR_D$ Found | $MR_D$ Calc. | Exaltation |
|---|---|---|---|---|---|---|
|  | 117.5-118.5° | 1.0573 | 1.5338 | 40.53 | 38.71 | 1.82 |
|  | 128.0-128.5 | 1.0356 | 1.5300 | 45.31 | 43.33 | 1.98 |
|  | 149.0-151.0 | 0.9967 | 1.5152 | 54.45 | 52.57 | 1.88 |

TABLE 2

| Acetate | Boiling points at 20 mm | $d_4^{20}$ | $n_D^{20}$ | $MR_D$ Found | $MR_D$ Calculated | Exaltation |
|---|---|---|---|---|---|---|
|  | 126.0-127.0° | 1.0607 | 1.5050 | 50.30 | 48.08 | 2.22 |
|  | 132.0-134.0 | 1.0412 | 1.5028 | 55.02 | 52.69 | 2.33 |
|  | 154.0-156.0 | 1.0067 | 1.4958 | 64.35 | 61.93 | 2.42 |

The freshly distilled alcohol was an oil-like, light-yellow liquid with an individual odor.

0.1007 g substance: 0.2610 g $CO_2$; 0.0687 g $H_2O$. Found%: C 69.13. $C_8H_{10}O_2$. Calculated %: C 69.56; H 7.30.

Upon the dehydration of γ-furyl-α-methylallyl alcohol with phosphorus pentoxide or iodine, a brittle, wine-red tar, transparent in thin layers, was obtained.

2. Preparation of γ-furyl-α-ethylallyl alcohol. 7.3 g (0.3 mole) of fine magnesium shavings, 32.7 g (0.3 mole) of ethyl bromide, and 24.4 g (0.2 mole) of furylacrolein were used for the synthesis. The same conditions

were used for the reaction as for the preparation of γ-furyl-α-methyl alcohol.

B.p. 128.0-128.5° at 20 mm. Yield 72.10% γ-furyl-α-ethylallyl alcohol was a light-yellow, oil-like liquid.

0.1478 g substance : 0.3862 g $CO_2$; 0.1048 g $H_2O$. Found %: C 71.29; H 7.93. $C_9H_{12}O_2$. Calculated %: C 71.03; H 7.95.

3. Preparation of γ-furyl-α-n-butylallyl alcohol. The alcohol was obtained from 7.3 g (0.3 mole) of magnesium, 27.8 g (0.3 mole) of normal butyl chloride, and 24.4 g (0.2 mole) of furylacrolein using the above conditions for conducting the reaction.

B.p. 149.0-150.0° at 20 mm. Yield 73.10%. Light yellow, glycerol-like liquid.

0.1341 g substance: 0.3596 g $CO_2$; 0.1046 g $H_2O$. Found %: C 73.16; H 8.73. $C_{11}H_{16}O_2$. Calculated %: C 73.33; H 8.95.

II. Synthesis of acetates of γ-furyl-α-alkylallyl alcohols.

1. Preparation of γ-furyl-α-methylallyl acetate. 13.8 g (0.1 mole) of the alcohol, 15.8 g (0.2 mole) of dry pyridine, and 10 ml of dry benzene were placed in a small, wide necked flask. The flask was closed with a stopper which contained a thermometer, calcium chloride tube, and a dropping funnel with a calcium chloride tube. The mixture of products was cooled below zero and then 11.8 g (0.15 mole) acetyl chloride was added to it dropwise with continuous stirring from the dropping funnel. The latter was added at such a rate as to keep the temperature of the reaction mixture from rising above +10°. After the addition of all the acetyl chloride, the reaction flask was left in the cooling mixture with intermittent mixing of the contents for 1 hour more. In order to attain a more complete esterification reaction, the mixture was allowed to stand at room temperature for half a day. The precipitated pyridine hydrochloride was dissolved in the minimum amount of water. The benzene layer of the acetate was separated from the water layer, washed with a dilute sodium bicarbonate solution, then with water, and dried with sodium sulfate. The benzene was removed on the water bath using a slight vacuum. γ-Furyl-α-methylallyl acetate vacuum distilled (20 mm) at 126.0-127.0°. Yield 69.10-75.5%. Oil-like (more fluid than the alcohol) light liquid. On storage, the yellow color of the ester intensified gradually and then became dark red.

The analysis of the ester was effected by saponification with titrated alcoholic sodium hydroxide solution. The saponification occurred upon weakly refluxing the alcohol for 2 hours. A blank experiment was made at the same time. 0.9768 g substance: 27.0 ml NaOH (T 0.008002). Found %: $CH_3CO$ 23.75. $C_8H_9O_2(COCH_3)$ Calculated %: $CH_3CO$ 23.89.

When the alcohol was acetylated with acetic anhydride under the same conditions, γ-furyl-α-methylallyl acetate with the above constants was obtained. Yield 55.3-60.4%.

2. Preparation of γ-furyl-α-ethylallyl acetate. 7.6 g (0.05 mole), 7.9 g (0.1 mole) of dry pyridine, 5 ml of dry benzene, and 5.9 g (0.075 mole) of acetyl chloride were used for the synthesis of the ester. The reaction was conducted under the same conditions as for the preparation of γ-furyl-α-methylallyl acetate. B.p. 132.0-134.0° (20 mm). Yield 82.0%.

0.9116 g substance: 23.48 ml NaOH (T 0.008002). Found %: $CH_3CO$ 22.17. $C_9H_{11}O_2(COCH_3)$. Calculated %: $CH_3CO$ 22.17.

3. Preparation of γ-furyl-α-n-butylallyl acetate. The ester was prepared from 9.0 g (0.05 mole) of the alcohol, and 5.90 g (0.075 mole) of acetyl chloride in a mixture of 7.9 g (0.1 mole) of pyridine and 5 ml benzene. The synthesis was effected as above. B.p. 154.0-156.0° (20 mm). Yield 81.50%.

0.8524 g substance: 19.15 ml NaOH (T 0.008002). Found %: $CH_3CO$ 19.34. $C_{13}H_{20}O_2(COCH_3)$. Calculated %: $CH_3CO$ 19.36.

## SUMMARY

1. γ-Furyl-α-methyl, γ-furyl-α-ethyl-, and γ-furyl-α-n-butylallyl alcohols were obtained from γ-furylacrolein by means of the organo-magnesium synthesis.

2. The acetates of the synthesized γ-furyl-α-alkylallyl alcohols were obtained by the action of acetyl chloride in pyridine.

3. It was shown that the γ-furyl-α-alkylallyl alcohols and their acetates on storage (especially in open vessels) are capable of gradually changing into thick, viscous products.

4. Brittle tar like products are formed upon the dehydration of the γ-furyl-α-alkylallyl alcohols with phosphorus pentoxide and with iodine.

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• See Consultants Bureau English Translation, p. 663.

# ALKALOIDS OF THE PAPAVERACEAE FAMILY

## XI. OXIDATION OF ISOTHEBAINE

V. V. Kiselev and R. A. Konovalova

In the previous communication on the structure of isothebaine [1], it was shown that the previously accepted proposal on the distribution of the substituents in isothebaine was not true. Contrary to the above, the paper of Schlittler and Muller [2] reports results which support the earlier accepted formula of isothebaine (I). These authors synthesized a trimethoxyphenanthrene with m.p. 78.5°, picrate m.p. 159°. They assigned the structure 3,4 ,5-trimethoxyphenanthrene to this substance. On determining the melting point of mixtures of synthetic trimethoxyphenanthrene and its picrate with that obtained after the decomposition of isothebaine, Schlittler and Muller did not find any depression; on the basis of this they came to the conclusion that the final product of the decomposition of isothebaine is 3,4,5-trimethoxyphenanthrene, and therefore, the previously proposed structure of isothebaine is true. However, according to older literature results, 3,4,5-trimethoxyphenanthrene melts at 90° [3], and its picrate at 166-167° [3,4]. Schlittler and Muller do not explain the difference between the melting point reported by them and that given in the previous paper. In view of the above, the authors do not agree with the conclusion of Schlittler and Muller relative to the structure of isothebaine.

In order to investigate further the question of the position of the substituent groups in isothebaine, the oxidation of isothebaine was effected with potassium permanganate in acetone. As result of this reaction, 3-methoxyphthalic acid was obtained. Therefore, there is only one methoxy group in the benzene ring (formula II), located in the ortho position to carbon atoms 11 and 12. Therefore, the hydroxyl and the second methoxy group must be present in benzene ring B, and formula (I) is excluded because it does not correspond to the properties of isothebaine. If Position 1 is rejected for the methoxy group in ring A as being improbable because substances with substituents in this position are not found in the aporphine series of alkaloids, only Position 4 remains for it.

An attempt was made to try and confirm the distribution of the substituents of ring B by the oxidation of methylated isothebaine, thus to obtain dimethoxyhemimellitic acid from ring B, but again 3-methoxyphthalic acid and an acid of composition $C_{18}H_{16}O_9$, which apparently was trimethoxydiphenyltricarboxylic (III), were obtained.

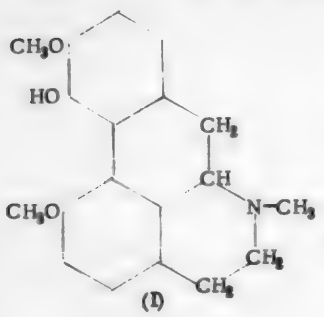
Apparently the benzene ring B of methylated isothebaine is less stable to oxidation with permanganate than ring A. For comparison, an experiment was conducted on the oxidation of methylated corydine, in which the substituted hemimellitic acid once more could not be isolated. In place of the latter, an acid of the composition $C_{19}H_{18}O_{10}$ was obtained which must have the structure 5,6,5',6'-tetramethoxydiphenyl-2,3,3'-tricarboxylic acid (IV).

These results on the oxidation of methylated isothebaine and corydine agree with the results of a series of other investigations on the oxidation of aporphine alkaloids [5]. Therefore, evidently, a common property of the non-phenolic alkaloids of the aporphine series is the increase in the stability of ring A to oxidation by permanganate in comparison to Ring B.

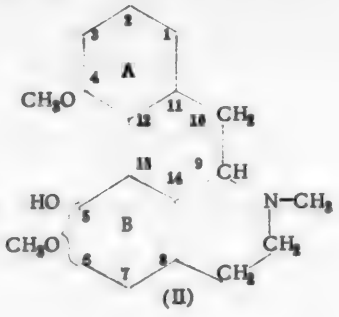
## EXPERIMENTAL

Oxidation of isothebaine. 3-Methoxyphthalic anhydride. 3 g of isothebaine was dissolved in 15 ml of 1 N $H_2SO_4$, the solution diluted with 80 ml of water, and the excess acid neutralized with 1 N NaOH. Then 21.9 g of potassium permanganate in 675 ml of water was added stepwise with stirring to the solution. At first the oxidation was conducted at room temperature, and after the decolorization slowed down, it was heated on the water bath to 50-60°. At this temperature, the addition of the oxidizing agent was continued until the color of the permanganate remained stable for 1 hour. The excess permanganate was decolorized by the addition of a small amount of sodium sulfite. The manganese dioxide was filtered and washed with hot water. The mother

liquor, combined with the wash water, was acidified with strong hydrochloric acid, evaporated in vacuum to a volume of 25-30 ml, and extracted with ether. The ether extract, after drying over sodium sulfate, was evaporated. Weight of the residue, 1.91 g. From the residue, 0.68 g of a sublimate was obtained at 2 mm and 155-170°, which gave 0.31 g of a yellow crystalline substance with m.p. 156-157° upon recrystallization from 4 ml of toluene. After two recrystallizations from toluene, m.p. 159-160°. The substance is almost insoluble in cold water. Hot water rapidly dissolves it but on cooling crystallization does not occur; the reaction of the aqueous solution is acid to litmus and, weakly so, to Congo. Methyl and ethyl alcohols dissolve the substance with difficulty; upon boiling the solutions acquire an acidic reaction. The substance is difficultly soluble in benzene and toluene.



(I)



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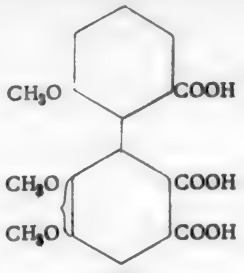

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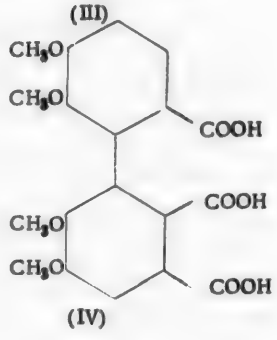

(IV)

The isolated anhydride did not give a depression in melting point upon mixing with 3-methoxyphthalic anhydride (m.p. 159.5-160°), obtained by the oxidation of 1,5-dimethoxynaphthalene. The melting point of the mixture, 159-160°. According to the literature, the melting point of 3-methoxyphthalic anhydride is 160-161° [6].

Aniline acid from 3-methoxyphthalic anhydride. 0.07 g of 3-methoxyphthalic anhydride was dissolved in 3 ml of hot toluene. A solution of 0.05 g of aniline in 0.5 ml of toluene was added to it. After some time, the whole solution was transformed into a continuous mass of fine, colorless crystals. 0.09 g was isolated. After recrystallization from 50% alcohol, 0.06 g of colorless platelets was obtained; upon slow heating, the m.p., 159-160°, upon rapid heating, the substance melted with frothing at 163°. After the solidification of the droplet, and heating once more, m.p. 187-189°. A sample of 3-methoxyphthalic acid and the mixture melted at 163° with frothing on rapid heating. Upon further heating, after the droplet solidified, the sample and the mixture melted at 187-190°. According to the literature, 3-methoxyphthalanilic acid melts at 164° with the formation of 3-methoxyphthalanil which has the m.p. 188 5-190° [6].

Oxidation of methylated isothebaine. 4.35 g of isothebaine methyl methosulfate was dissolved in water. A 3-4% solution of potassium permanganate containing 21.84 g of $KMnO_4$ was gradually added. The oxidation was conducted at 60-70° with stirring; when the oxidation slowed down, the temperature was raised to 80-85°, and the permanganate added until the color of the mixture remained stable for 1 hour. The excess permanganate was decolorized with sodium sulfite. The manganese dioxide was filtered and washed with hot water. The mother liquor and the water washings were evaporated in vacuum to a volume of 15-20 ml. The evaporated solution, after acidification with strong sulfuric acid, was extracted with ether. The ether extract, after drying over sodium sulfate, was evaporated. The residue was mixed with 20 ml of 20% potassium hydroxide. The solution was heated for one hour on the water bath, and then acidified and extracted with ether. After the evaporation of the ether extract, 2.1 g of a yellow tar was obtained, which was dissolved in 4.5 ml of water. Upon standing, 0.58 g of a slightly yellow crystalline acid separated from the solution. It melted at 240-241° upon slow heating; upon rapid heating, m.p. 175-180° with frothing, whereupon the substance crystallized immediately and melted once more at 240-241°. After recrystallization from water, the substance decolorized and melted without change. It is readily soluble in ethyl and methyl alcohol, slightly soluble in hot water, and very difficultly soluble in cold water and benzene. Aqueous solutions gave a weakly acidic reaction on Congo. Small amounts of the substance, initially heated to 210°, gave a green fluorescence in a dilute sodium bicarbonate solution, which disappeared upon standing. In a saturated solution of sodium bicarbonate, the fluorescence was barely

noticeable and vanished rapidly; it vanished immediately upon the addition of acids or alkalies.

3.932 mg substance: 8.341 mg $CO_2$; 1.486 mg $H_2O$. 2.646 mg substance: 5.622 mg $CO_2$; 1.029 mg $H_2O$. 15.30 mg substance: 7.20 ml 0.1 N. $Na_2S_2O_3$. 18.75 mg substance: 8.88 ml 0.1 N. $Na_2S_2O_3$. Found %: C 57.85, 57.95; H 4.23, 4.35; $OCH_3$ 24.33, 24.48. $C_{18}H_{16}O_9$. Calculated %: C 57.47; H 4.26; 3 $OCH_3$ 24.73.

From the mother liquor, 0.10 g of the same, impure substance and 0.22 g of 3-methoxyphthalic anhydride were isolated.

Methylation of corydine. Corydine methyl ether methylmethosulfate. 4 g of corydine hydrochloride was mixed with 21 ml of 30% sodium hydroxide. 12.8 g of dimethyl sulfate was added to the mixture which was then slowly heated on the water bath, the saponification of dimethyl sulfate then became noticeable; when the reaction became somewhat violent, the flask had to be cooled with cold water. The mixture was transformed into a thick, white mass. The crystalline precipitate was filtered and washed with alcohol. After two recrystallizations from alcohol, 3.16 g of a substance with an m.p. of 247-248° was obtained. The crystals—shiny, white scales. Corydine methyl ether methylmethosulfate did not give a color reaction with ferric chloride; upon mixing aqueous solutions of the methylmethosulfate and potassium permanganate, a white precipitate formed.

Corydine methyl ether methiodide. Upon mixing an aqueous solution of the methylmethosulfate with an excess of a saturated solution of potassium iodide, the methiodide came out in the form of a finely crystalline precipitate. After two recrystallizations from alcohol, a methiodide with an m.p. 248-249° (with decomp.) was obtained.

Oxidation of methylated corydine. 5,6,5',6'-Tetramethoxydiphenyl-2,3,3'-tricarboxylic acid. 2.05 g of corydine methyl ether methylmethosulfate was dissolved in water. A solution of potassium permanganate was added to the solution under the same conditions as for the oxidation of methylated isothebaine. A total of 320 ml of an aqueous solution containing 11.52 g of potassium permanganate was consumed. The manganese dioxide was washed with hot water after filtration. The mother liquor and the water washes were combined and evaporated to a volume of 10-15 ml. After acidification with 3.5 ml of strong hydrochloric acid, a yellowish, crystalline precipitate formed which weighed 0.03 g. M.p. 195-200° with frothing. This substance was not investigated further. The acidic mother liquor was extracted with ether. 0.54 g of a colorless tar was obtained from the extracts. The tar was dissolved in 1.5 ml of water, and upon standing, 0.15 g of a substance crystallized which became fluid at 100°. After drying at 60-70°, the substance melted at about 125°, frothed, and at the same time, solidified. Upon further heating, the substance melted at 229-230.5°. If the substance was heated slowly, starting at 100°, it shrank at 120-125°, and at 229-230.5° it melted. After one recrystallization the melting point of the substance, well dried by slowly heating to 100°, was 230-231°.

15.25 mg substance: 8.7 ml 0.1 N $Na_2S_2O_3$. 11.70 mg substance: 6.7 ml 0.1 N $Na_2S_2O_3$. Found %: $OCH_3$ 29.49, 29.61. $C_{19}H_{18}O_{10}$. Calculated %: 4 $OCH_3$ 30.56.

## SUMMARY

1. Upon the oxidation of isothebaine with permanganate, 3-methoxyphthalic acid was obtained. This showed the positions of the hydroxyl and methoxyl to be in the benzene ring of the tetrahydroisoquinoline nucleus of the aporphine skeleton. There is one methoxyl in the other benzene ring attached to position 1 or 4.

2. A common property of the non-phenolic alkaloids of the aporphine series was that the benzene ring of the tetrahydroisoquinoline nucleus was less stable, than the other benzene ring of the given aporphine derivative, to oxidation with permanganate in basic media.

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*See Consultants Bureau English Translation, p. 135.

# ALKALOIDS FROM THE BRANCHY PLANTAIN

## (PLANTAGO INDICA)

A. Danilova and P. Konovalova

The branchy plantain (Family Plantagenae) is an annual, grasslike plant prevalent in the Caucasus and the European part of the U.S.S.R. It was gathered by the Botanical Expedition of the All-Union Scientific Research Institute of Pharmaceutical Chemistry (VNIKhFI) under the leadership of P. C. Massagetov in July 1948, on sandy banks of the Khram River (Georgian S.S.R.).

The plantain has been known for a long time in folk medicine as a remedy for the healing of cuts and wounds, and for curing tuberculosis and dysentery. It is not surprising that this plant attracted the attention of various invetigators, who discovered glycosides, enzymes, organic acids, choline, and adenine in the plantain. However, there are no papers in the literature on the presence of alkaloids in the plantain.

The underground parts of the branchy plantain were investigated. Upon the extraction of the plant with dichloroethane in the usual manner, a mixture of alkaloids in 0.25% quantity based on the weight of the air dried plant was obtained. The separation of these alkaloids presented certain difficulties, and only after a great number of experiments could three individual alkaloids be isolated, which were new substances, unreported in the literature.

The first crystalline alkaloid was obtained in a small amount: it is proposed that it be called plantagonin. Its analysis suggests the formula $C_{10}H_{11}O_2N$. Plantagonin separates from an ether solution in the form of needles, gathered into clusters. After recrystallization from acetone, it melted at 218-220°; $[\alpha]_D$ + 30.8 (1.1% HCl). It is poorly soluble in water and in organic solvents. It forms a picrate with m.p. 159-160°, a hydrochloride with m. p. 228-230°, ', and a chloroaurate with m.p. 151-152°. Plantagonin contains a hydroxyl group; neither a methoxyl group nor' a methylimidyl group were detected.

The second alkaloid which was called indicamin, was a steam volatile liquid. Indicamin distills in vacuum at 75-92° (0.4 mm) in the form of a colorless liquid, discoloring slightly in the air, with a strongly expressed, basic odor. Its composition approximates the formula $C_{14}H_{23}ON$. It gives a picrate crystallizing from alcohol with m.p. 127-129°. Indicamin is an unsaturated base, and immediately decolorizes potassium permanganate in the cold.

The third alkaloid – indicain – has the composition $C_{10}H_{11}ON$. It is liquid base, volatile with steam. Indicain distills in vacuum at a somewhat higher temperature (b.p. 92-105). Its picrate melts at 151-153° after recrystallization from ethyl acetate.

A more detailed study of the alkaloids separated was not undertaken because of an insufficient quantity of the plant.

## EXPERIMENTAL

1. Separation of total alkaloids. 14 kg of the dried, finely ground plant was moistened with 10% ammonia, and exhaustively extracted with dichloroethane. The alkaloids were extracted from the dichloroethane solution with 10% sulfuric acid The acid solution was filtered, cooled, and made alkaline with 25% ammonia. The alkaloids were extracted from the alkaline solution with ether at the start and then with chloroform.

2. Isolation of alkaloids from the ether solution. Upon standing, crystals gathered into clusters, separated from the ether solution of the alkaloid on the bottom and the sides of the flask. The crystalline substance was filtered, washed with acetone, and dried at 60°. The crystalline base, called plantagonin by the authors, weighed 1.22 g. After two recrystallizations from acetone (1:100), m.p. 218-220°, weight 0.6 g. A portion of the substance was recrystallized from 96% alcohol; the melting point did not change.

Plantagonin is poorly soluble in water and organic solvents, and completely insoluble in benzene. Upon

heating it dissolved in water, chloroform, ethyl acetate, and alcohol. A sulfuric acid solution of plantagonin did not decolorize permanganate. Plantagonin is an optically active base.

0.2206 g substance: in 4 ml 1.1% HCl: $\alpha_D$ + 0.85; $[\alpha]_D$ + 30.8° where $\underline{l}$ = 0.5 dm.

4.190 mg substance: 10.466 mg $CO_2$; 2.32 mg $H_2O$. 6.03 mg substance: 0.412 ml $N_2$ (21.5°, 745 mm). Found %: C 68.12; H 6.19; N 7.76. $C_{16}H_{11}O_2N$. Calculated %: C 67.79; H 6.21; N 7.90.

Plantagonin hydrochloride. The base was dissolved in an alcoholic hydrogen chloride solution and precipitated with ether. The precipitated hydrochloride was filtered and washed with water. After two reprecipitations, the hydrochloride melted at 228-230° with decomposition.

2.698 mg substance: 1.778 mg AgCl. Found %: Cl 16.30. $C_{16}H_{11}O_2N \cdot HCl$. Calculated %: Cl 16.62.

Plantagonin picrate. 0.05 g of plantagonin was dissolved with heating in 3 ml of water; a saturated aqueous solution of picric acid was added to the cooled solution. A finely crystalline powder separated from the mixed solutions upon standing. This powder was filtered, washed with water, and dried at 60°. After two recrystallizations from water, m.p. 159-160°.

4.035 mg substance: 0.518 ml $N_2$ (22°, 732 mm). Found %: N 14.31. $C_{16}H_{11}O_2N \cdot C_6H_3O_7N_3$. Calculated %: N 13.79.

Plantagonin chloroaurate. 0.05 g of plantagonin was dissolved in 3 ml of 10% hydrochloric acid, and 0.3 ml of an aqueous $HAuCl_4$ solution was added to it. Oil-like droplets separated from the mixture, which dissolved upon heating on the water bath. Upon slowly cooling, needle-like crystals of the chloroaurate separated. After recrystallization from dilute hydrochloric acid, m.p. 151-152°.

4.782 mg substance: 1.812 mg Au. Found %: Au 37.89. $C_{16}H_{11}O_2N \cdot HAuCl_4$. Calculated %: Au 38.12.

Plantagonin formed a crystalline methiodide without a clear melting point, and which was very difficult to purify.

Isolation of the liquid alkaloids. The ether solution, after the removal of the crystalline alkaloid, was shaken several times with 10% sodium hydroxide, and then washed with water and dried over $Na_2SO_4$. After the removal of the ether, 27.8 g of liquid bases was obtained. The alkaloids obtained were steam distilled. The steam volatile bases distilled in the form of oily droplets immiscible with water. The distillate was extracted with ether. The ether solution was dried over $Na_2SO_4$. After the removal of the ether, 1.46 g of liquid alkaloids with a characteristic odor was obtained.

The residue in the flask after the removal of the volatile bases, consisted of two layers, a tarry layer and a clear aqueous layer. No pure alkaloids could be isolated from the tarry layer. A saturated aqueous solution of picric acid was added to the aqueous layer. A crystalline precipitate separated from the mixture upon standing. After two recrystallizations, first from alcohol and then from ethyl acetate, a picrate with m.p. 149-150° was obtained. From the mother liquor, a small amount of a picrate was isolated which melted at 124-127° after recrystallization from alcohol.

The liquid bases (1.46 g) were vacuum distilled (0.4 mm). Two fractions were collected: with b.p. 75-92° (0.57 g) and with b.p. 92-105° (0.5 g).

Indicamin. A picrate was obtained from the first fraction with an alcoholic picric acid solution, which melted at 127-129° after many recrystallizations from alcohol. The picrate is readily soluble in ethyl acetate, dioxane, acetone, and chloroform, and poorly soluble in water.

3.485 mg substance: 6.810 mg $CO_2$; 1.749 mg $H_2O$. 4.026, 4.148 mg substance: 0.428, 0.431 ml $N_2$ (20°, 16°, 744.5, 752.2, mm). Found %: C 53.29; H 5.61; N 12.15, 12.16. $C_{14}H_{23}ON \cdot C_6H_3O_7N_3$. Calculated %: C 53.57; H 5.36; N 12.47.

Indicain. A picrate with m.p. 145-146° was obtained from the second, higher boiling fraction with an aqueous solution of picric acid. After three recrystallizations from ethyl acetate, indicain picrate melted at 151-153°.

3.686 mg substance: 6.693 mg $CO_2$; 1.196 mg $H_2O$. 3.656 mg substance: 0.464 ml $N_2$ (18.0°, 727.5 mm). Found %: C 49.52; H 3.63; N 14.25. $C_{16}H_{11}ON \cdot C_6H_3O_7N_3$. Calculated %: C 49.23; H 3.58; N 14.35.

Isolation of alkaloids from the chloroform solutions. 6 g of tarry, non-crystalline bases was obtained from the chloroform solution. Upon attempting to purify them by means of salts, it was found that the picrate, the tartrate, and the hydrochloride tarred upon the slightest heating.

The analyses were made at the microanalytical laboratory of VNIKhFI, directed by V. V. Kolpakova.

## SUMMARY

1. Three new alkaloids were isolated from the Caucasian branchy plantain: plantagonin, composition $C_{10}H_{11}O_2N$; indicamin, $C_{14}H_{23}ON$, and indicain, $C_{11}H_{11}ON$.

2. The Caucasian plantain is the first alkaloid-carrying representative of the family Plantagenae.

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# DISCUSSION

## ERRORS OF A.A.KALANDIYA IN HIS PAPER "COMPUTING THE MOLECULAR VOLUMES OF INORGANIC COMPOUNDS OF THE $A_nB_mO_s$ TYPE",* AND HIS ATTEMPTS TO SUPPORT THE ERRONEOUS RESONANCE CONCEPT

G. V. Tsitsishvili

The author of the paper cited, A.A.Kalandiya, proposed a formula for the calculation of molecular volumes of inorganic compounds of the $A_nB_mO_s$ type, and in conclusion wrote: " it should be stated that the theoretical considerations we have set forth here make it possible to compute the molecular volumes of compounds of the foregoing type accurately by means of the formula proposed by us."

Let us examine the basic steps of the "theoretical" discussion of A.A.Kalandiya, so that we may evaluate them and see whether or not A.A.Kalandiya was justified in making such an all-promising conclusion. For clearness, we will give an excerpt from the initial discussion of A.A.Kalandiya (see p. 1635 and 1636**): " To compute the molecular volumes of compounds of the foregoing type ($A_nB_mO_s$) we made use of the formula proposed by us to compute interatomic distances in compounds of this type.

"In brief, this is the solution of the latter problem. In accordance with Coulomb's law, the mutual attraction between the $B^{z+}$ and $O^{t}$ *** ions should be:

$$\frac{z_1 z_2 e^2}{r^2}.$$

" Now let us consider the instant when the anion $B_m O_s^{y-}$ and the cation $A_n^{x+}$ approach each other to the distance of the radius required for their mutual attraction and the $O_s^{f-}$ and $A_n^{x+}$ ions mutually attract each other. As $O_s^{f-}$ constitutes the intermediate bridge transmitting the mutual attraction of the $O_s^{f-}$ and $A_n^{x+}$ ions, on the one hand, and the attraction of the $O_s^{f-}$ and $B_m^{z+}$ ions on the other, the latter depends not only on the distance between them but also on the number of ions in the molecules and on the magnitude of their charges. For instance, in $NaClO_4$, the Cl — O distance equals 1.59 A; this distance is likewise 1.59 A in $KClO_4$; in $Ag_3PO_4$ the P — O distance is 1.61 ± 0.03 A; in $BPO_4$ this distance is 1.54 A, etc. Hence, the force of mutual attraction, $F_1$, between the ions of the anion $B_m O_s^{y-}$ when acted upon by the cation $A_n^{x+}$, from the empirical data cited above, must equal:

$$F_1 = \frac{Az_1 z_2 z_3 z_4 e^2}{r_1^2} \qquad (1)$$

"Owing to the fact that their charges are of like sign, the $A_n^{x+}$ and $B_m^{z+}$ ions repel each other, the force of mutual repulsion, $F_2$, equalling:

$$F_2 = \frac{Az_1 z_2 e^2}{r_2^2} \qquad (2)$$

"From Equations (1) and (2) it is apparent that the repulsive forces will be positive, and the attractive forces negative, as the former will exist for like signs on $z_1$ and $z_2$, and the latter exist for unlike charges. Hence, summing up, we find that the aggregate attractive force F must be:

$$F = F_1 + F_2 = -\frac{Az_1 z_2 z_3 z_4 e^2}{r_1^2} + \frac{Az_1 z_2 e^2}{r_2^2}, \qquad (3)$$

where F = attractive force of the foregoing ions; A = Madelung's constant, depending chiefly upon the number

* See Consultants Bureau English Translation, p. a-59 ff.

** See Consultants Bureau English Translation, p. a-59-a-61.

*** Here, obviously, it must be $O_s^{f}$.

of ions in the molecule; e = the charge on an electron; $z_1$ = the amount of charge employed for the bond with element A; $z_2$ = the amount of charge employed for the bond with element B; $z_3$ = the amount of charge employed for the bond with element O; $z_4$ = the amount of charge employed for the bond between element O and one element of the cation; $r_1$ = the distance between the $B_m^{z+}$ and $O_s^{f-}$ ions, i.e., $R_{z_2z_3}$; $r_2$ = the cation radius, $R_{z_1}$.

$$R_{z_1} + R_{z_2z_3} = R_{z_1z_2z_3}."$$

The style of Kalandiya will not be discussed here, only the essentials of the question. There is practically no basis for the expression for the attractive forces (see Equation 1). The introduction of the constant coefficient A, which Kalandiya glorifies as the 'Madelung Constant', has no basis here at all. The constant coefficient in the energy of attraction is a function of the type of lattice in the solid; it is usually used for the electrostatic calculation of the lattice energy. Here Kalandiya attempts to calculate the reaction between m positive ions B and s negative ions O. It is nowhere shown that the attractive force, $F_1$, is actually proportional to $z_3$ and $z_4$. It is appropriate to point out that in the foregoing foggy text, it is almost impossible to comprehend the significance of $z_1$, $z_2$, $z_3$, and $z_4$. For instance, Kalandiya writes that: "$z_1$ = the charge employed for the bond with element A." One must ask -- the value of what charge and, probably, employed, rather than occupied by, as the author writes:)* for the bonds of what ions (and not elements, as the author confuses it)?

The force of mutual attraction, $F_1$, according to Equation (1), is inversely proportional to $r_1^2$, with Kalandiya stating that $r_1$ = the distance between $B_m^{z+}$ and $O_s^{f-}$. It is obviously necessary to take into consideration the chemical structure when characterizing the distance between the complex cation and complex anion. Kalandiya did not trouble to do this, and characterized the distance between complex ions in the same manner as for simple ions.

Equation (2) for the force of repulsion is also baseless. How can the force of rupulsion between the ions $A_n^{x+}$ and $B_m^{z+}$ be inversely proportional to the square of the radius of the cation. It is impossible to understand how the first member of the right side of Equation (3) obtained its minus sign, since, according to Equation (1), $F_1 = \frac{Az_1z_2z_3z_4e^2}{r_1^2}$. Why does Equation (3), which should, evidently, express the aggregate attraction force, not take account of the reaction between the ions $A_n^{x+}$ and $O_s^{f-}$ ?

The author continues:

"The energy of formation of the anion $U_1$, arising as the result of the approaching of the ions (from infinity to the distance $R_{z_2z_3}$), will be:

$$U_1 = -\int_{\infty}^{R_{z_2z_3}} F_1 dr_1 = \int_{\infty}^{R_{z_2z_3}} \frac{z_1z_2z_3z_4e^2}{r_1^2}\, dr_1 = -\frac{z_1z_2z_3z_4e^2}{R_{z_2z_3}}.$$

"At the instant the ions with complete electron shells come into contact or approach each other, the force of repulsion, approximately equal to $B/R^n$, is generated; hence, the complete energy of interaction between the ions is:

$$U_1 = -\frac{Az_1z_2z_3z_4e^2}{R_{z_2z_3}^2} + \frac{B}{R_{z_2z_3}^n}. \qquad (4)$$

"Upon differentiation of this equation we get:

$$\frac{dU_1}{dR} = \frac{Az_1z_2z_3z_4e^2}{R_{z_2z_3}^2} - \frac{nB}{R_{z_2z_3}^{n+1}}\Big\rangle."$$

Kalandiya subsequently writes:

$$"R_{z_2z_3} = \sqrt[n-1]{\frac{nB}{Az_1z_2z_3z_4e^2}}. \qquad (5)$$

"Assuming that we are dealing with univalent elements, we find from Equation (5) that:

* The Russian word originally used by Kalandiya has various synonyms, and might be translated as: occupied by, busied with, employed for. In the translation of the Kalandiya paper discussed here, Consultants Bureau chose the latter translation as most probably conveying the author's meaning.

$$R_{11(z_1z_3)} = \sqrt[n-1]{\frac{nB}{Ae^2}} \quad . \quad \text{"} \qquad (6)$$

Kalandiya mechanically dissects the energy of interaction from the energy of attraction and repulsion. As a result of this, the repulsion force mysteriously arises for Kalandiya at the instant of the mutual approach of the ions.

Here Kalandiya also quite incomprehensibly takes the attraction force as equal to $-\frac{Az_1z_2z_3z_4e^2}{r_1^2}$, and not as he gives in the first formula.

Kalandiya expresses the repulsion force by means of the formula $\frac{B}{R^n}$ and, disregarding elementary rules on the addition of like dimensions, adds the repulsion force to the energy of attraction [see p. 1637, Equation (4)]*.

Kalandiya, on the basis of such self-formed "theoretical" material, where he uses, as he says "empirical" results, proposes a formula for the distance between the ions $B_m^{z+}$ and $O_s^{f-}$ [see p. 1637 equation (7)]: •

$$R_{z_1z_3} = \frac{R_{11(z_1z_3)}}{\sqrt[n-1]{z_1z_2z_3z_4}} \quad . \qquad (7)$$

Further Kalandiya writes:

"If we compute $F_2$ analogously from Equation (2), we get:

$$R_{z_1} = \frac{R_1(z_1)}{\sqrt[n-1]{z_1z_2}} \quad . \qquad (8)$$

"As was stated above, $R_{z_1} + R_{z_2z_3} = R_{z_1z_2z_3}$; hence, it follows from Equations (7) and (8) that:

$$R_{z_1z_2z_3} = \frac{R_{11(z_2z_3)}}{\sqrt[n-1]{z_1z_2z_3z_4}} + \frac{R_1(z_1)}{\sqrt[n-1]{z_1z_2}} \quad ,$$

i.e.,

$$R_{z_1z_2z_3} = \frac{R_{11(z_2z_3)} + \sqrt[n-1]{z_3z_4R_1(z_1)}}{\sqrt[n-1]{z_1z_2z_3z_4}} \quad . \qquad (9)$$

"We introduce the coefficient K of the coordination number to be expressed, and get:

$$R_{z_1z_2z_3} = K \cdot \left( \frac{R_{11(z_2z_3)} + \sqrt[n-1]{z_3z_4 R_1(z_1)}}{\sqrt[n-1]{z_1z_2z_3z_4}} \right) \quad . \qquad (10)$$

etc.".

Kalandiya, from the beginning of the above quotation, apparently set himself the goal of calculating $F_2$, but in reality, quotes the value of $R_{z_1}$. Of what accurate analogy does the author speak for the calculation of $F_2$ — it is uncertain. If the calculation of $F_2$ is effected as accurately as the calculation of $F_1$, then such accuracy cannot be imagined. How the value $R_{z_1}$ was obtained is unknown. The author evades this by silence. It is completely impossible to reconcile equations (9) and (10), where there are identical left parts of the equation and different right parts. Here the author again exceeds the limits of common mathematical rules, and uses his own mathematics. The suggestion "Introducing the coefficient K of the coordination number to be expressed" has no basis, and is not related to the preceeding text. As for equations (5) and (7) on page 1637, Kalandiya here attempts to account for the influence of foreign ions on the distance between the ions $B_m^{z+}$ and $O_s^{f-}$. Assuming that the ions are monovalent, he obtains for $R_{11(z_2z_3)}$ the well-known expression for the radius of a monovalent ion. Therefore, it is clear that if the foreign ions possess a single charge, they have

• See p. 1639. (p. a-61 and a-62 in English translation).

no influence. The effect of the foreign ions on the above distance must, evidently, decrease as a function of the decrease in the charges; in other words, $R_{z_2z_3}$ must approach $R_{11(z_2z_3)}$ when the charge on the foreign ion approaches zero. What have we in reality? It is not difficult to see that, when the denominator approaches zero, the expression for $R_{z_2z_3}$ approaches infinity. The result, as in the previous case, is obviously absurd.

Kalandiya continues with a foggy discussion on the coefficient of repulsion and proposes some sort of "mixed" calculation, which he does not explain further. We quote again from Kalandiya's paper: "As we are of the same opinion: that the effective radius of atoms or ions is the starting point for computing molecular volume, computing the magnitude of molecular volume of compounds of the type mentioned requires the interatomic distance derived from Equation (10), proposed by us for determining the interatomic distance between the centers of the anion and cation, multiplied by the coefficient A and by $10^{-8}$ [for compounds of the $A_2(BO_4)_3$ type, coefficient A is 1.5, and equals unity for all the other compounds investigated by us]. The result is then cubed and multiplied by PN, i.e., by the number of atoms or ions (P) that make up the molecule, and by Avogadro's number (N), after which it is divided by the sum of the ratio of the interatomic distance of the compound considered to the interatomic distance of the anion plus the coefficient of repulsion, $\underline{n}$ (= 9), multiplied by the constant $\underline{1}$ (= 0.1).

"Thus, the formula proposed by us for computing the molecular volume finally takes on the following form:

$$V = \frac{\left[\left(\frac{R_{11(z_2z_3)} + \sqrt[n-1]{z_3z_4}\cdot R_{1(z_1)}}{\sqrt[n-1]{z_1z_2z_3z_4}}\right) KA10^{-8}\right]^3 PN}{\frac{1}{\underline{n}}\cdot\left\{n+\left[\left(\frac{R_{11(z_2z_3)} + \sqrt[n-1]{z_3z_4}\cdot R_{1(z_1)}}{\sqrt[n-1]{z_1z_2z_3z_4}}\right) KA10^{-8} : \frac{R_{1(z_2z_3)}}{\sqrt[n-1]{z_1z_m}}\cdot 10^{-8}\right]^3\right\}},$$

where $z_m$ = the aggregate sum of the charges employed for bonds with the ions (or atoms) that are interconnected with the central ion. Thus, for instance, anions of the $XO_3^{y-}$ type, the aggregate sum of the charges employed by the $O^{--}$ ion for bonds to the central ion (or atom) as well as to the cation equals 6, while it equals 8 for anions of the $XO_4^{y-}$ type, 8 for anions of the $X_2O_4^{y-}$ type, 14 for anions of the $X_2O_7^{y-}$ type, and this sum is taken by us as equal to unity for $(CN)^-$ and $(NH_4)^+$, respectively."

From this text it is seen that Kalandiya proposes a formula for the calculation of molecular volume, but in no way bases it on physical considerations. Here she uses a series of arbitrary coefficients and formulas for molecular volume, given always in complicated form. Kalandiya tried to give an impression of solidity to the formulas for molecular volume, without consideration for either chemical or physical bases. There is an algebraic absurdity in the formula itself, which it is pointless to discuss here.

For the application of the above formula, Kalandiya calculates molecular volumes. We quote the text of Kalandiya concerned with the calculation, and then we will return to the calculation itself: "Solving an example by means of the formula proposed by us for computing molecular volume is done as follows. Let us take as an example $NaIO_4$, for which $\underline{n}$ averages 7; $R_{11(z_2z_3)} = 0.77\ A + 1.76\ A$; $R_{1(z_1)} = 0.98\ A$; $z_1 = 1$; $z_2 = 7$; $z_3 = 2$; $z_4 = 1$; and $z_m = 8$; the coefficient K, expressing the coordination number, equals 1.044; the number of atoms entering into the composition of the molecule is 6; and coefficient A = 1. Hence,

$$V = \frac{\left[\left(\frac{0.77 + 1.76 + \sqrt[6]{2\cdot 1\cdot 0.98}}{\sqrt[6]{1\cdot 7\cdot 2\cdot 1}}\right)\cdot 1.044\cdot 10^{-8}\right]^3 \cdot 6\cdot 6.06\cdot 10^{23}}{0.1\left\{9+\left[\left(\frac{0.77 + 1.76 + \sqrt[6]{2\cdot 1\cdot 0.98}}{\sqrt[6]{1\cdot 7\cdot 2\cdot 1}}\right)\cdot 1.044\cdot 10^{-8} : \frac{0.77 + 1.76}{\sqrt[6]{1\cdot 8}}\cdot 10^{-8}\right]^3\right\}} = 51.0\ \text{ml}.$$

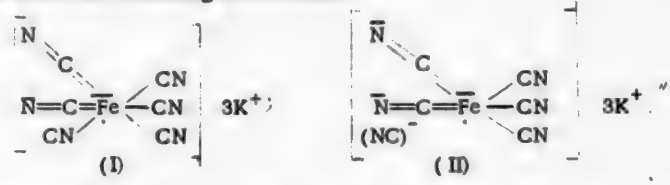
"The answer should have been 51.1 ml. Hence, the error is 0.1 ml, i.e., the agreement is extremely good.". It is strange that the meaning of the value K is not clarified in the text. K, according to Kalandiya, "is the coefficient of the coordination number to be expressed" (see the first line of p. 1639). In the text K is also used to designate the coordination number, the author stating that she used the values given by Zachariasen. Which does K represent – the coordination number or a function of it? It is generally difficult to discuss a puzzle of this sort. It is impossible to understand why Kalandiya used K = 1.044 for $NaIO_4$. Almost nothing is given as the basis of the value of the coefficient A, which Kalandiya takes to

equal unity in the case of $NaIO_4$.

In the formula for molecular volume (why is this formula without a number?), Kalandiya states that he takes the repulsion coefficient as 9. When he returns to the calculation of the $NaIO_4$ example, she assumes that it "averages 7" Here Kalandiya once more withdraws into his usual terminological fog. What is meant by the "average" repulsion coefficient, and, strictly speaking, on the basis of what data does Kalandiya take it to be 7 for $NaIO_4$, 7.3 for $NaBrO_3$, and 8.3 for $CoWoO_4$ and 9.3 for $PbMoO_4$ (see p. 1641, Table 3)*, etc. Surprisingly, when she turns to the calculation itself, which according to the above-cited statements must employ the value of $\underline{n} = 7$ for the case of $NaIO_4$, this value now becomes 9 and not 7. If $\underline{n}$ is taken as equal to 7 (in accordance with the text and Table 3), the value obtained for the molecular volume, V, is not 51.5 ml. V, for $\underline{n} = 7$, is about 63, not milliliters, but $63 \cdot 10^{24}$ ml. After all these operations, Kalandiya "obtains" the value 51.0 for the molecular volume of $NaIO_4$* which he states is close to the experimental value for the molecular volume. On the basis of what data the molecular volume value was obtained is not cited, of course "for clarity". Apparently, this calculation, the secret of whose operation is known only to Kalandiya, is scarcely of any use,

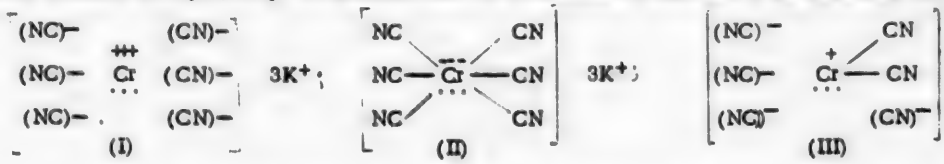
Kalandiya, undaunted, proposed to apply his formula further, for calculation of the molecular volume to complex compounds. Here Kalandiya states:

"Let us take, for example, $K_3Fe(CN)_6$, the structure of which is represented, according to Ya. K. Syrkin and M. E. Dyatkina**, by one of the following two variants:



(I) (II)

Kalandiya calculated the molecular volume for both "variants" (Kalandiya expression) of potassium ferrocyanide, and came to the specific conclusion that " in the foregoing compound, the structure is better expressed as the first variant" (see page 1643)***. The author further analyzes, from the same position, the coordination compounds, in particular $K_3Cr(CN)_6$. Here he writes: " Even more interesting are the results obtained for $K_3Cr(CN)_6$. Its structure may be represented by any one of the following thre variants:



(I) (II) (III)

"According to Ya. K. Syrkin and M. E. Dyatkina, the existence of structures such as those expressed by the first and second variants is allowable under the concept of their being mutually superposed on one another." Kalandiya once more, in his own way, calculates the molecular volume, and finally comes to the conclusion: "It must be assumed that the structure assigned to $K_3Cr(CN)_6$ by Ya. K. Syrkin and M. E. Dyatkina in the second variant predominates over all the other structures expressed by the other variants in the state of mutual superposition of one over another."

It is not difficult for the reader to see that all of the foregoing arguments of Kalandiya result in the anti-Butlerov representation of multi-structureness of molecules, and in a defence of the highly erroneous and methodologically defective, idealist concept of resonance. Kalandiya uses his "theoretical considerations" on molecular volumes to demonstrate that non-existent, fictious structures exist and possess the properties of compounds.

It is easy to see from the text that Kalandiya did not find time to study the literature on the question of molecular volume. He indicates that its history began with Bilts. Kalandiya would have found very enlightening the Journal of the Russian Physico-Chemical Society", as well as the wealth of Soviet chemical literature and other native sources. Kalandiya completely fails to relate the properties of a compound to its chemical structure. He has not taken into consideration Butlerov's theory of chemical structure. Kalandiya, in his paper which contains elementary and obvious physical and mathematical errors, is a defender of the scientifically insolvent and methodologically defective, idealistic concept of resonance.

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* See Consultants Bureau English Translation, p. a-66.

** In the Journal, thereis an obvious typographical error, as the molecular volume is given as 5.10 ml. (This misprint was not repeated in the English translation. Publisher.)

*** The Chemical Bond and the Structure of Molecules, Syrkin and Dyatkina, State Chemical Press.

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